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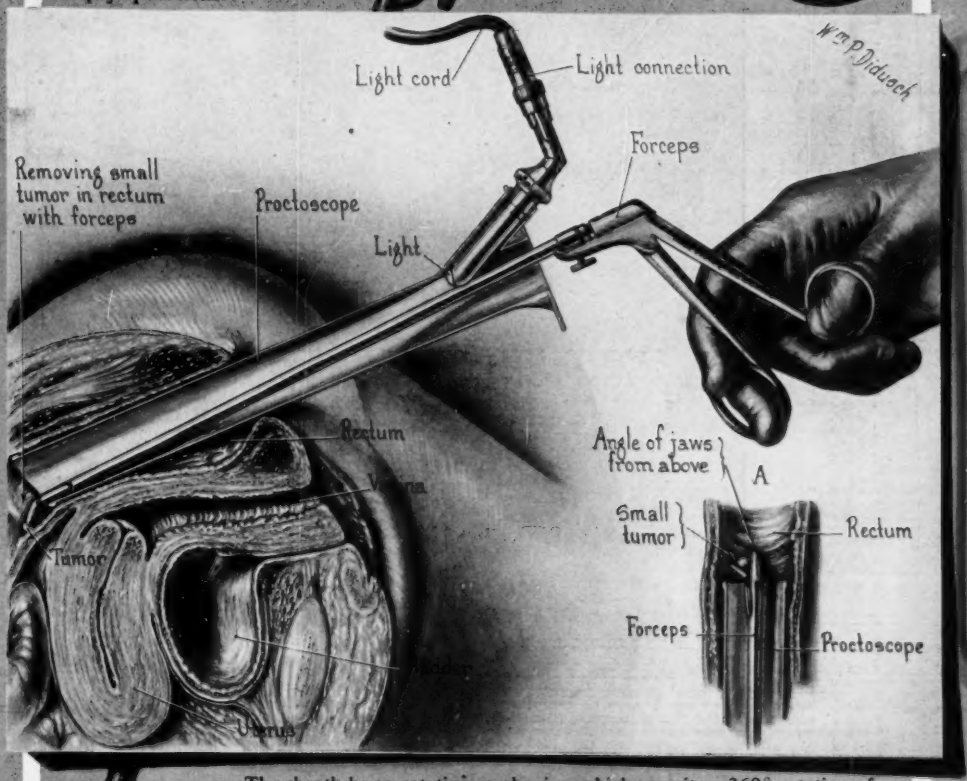

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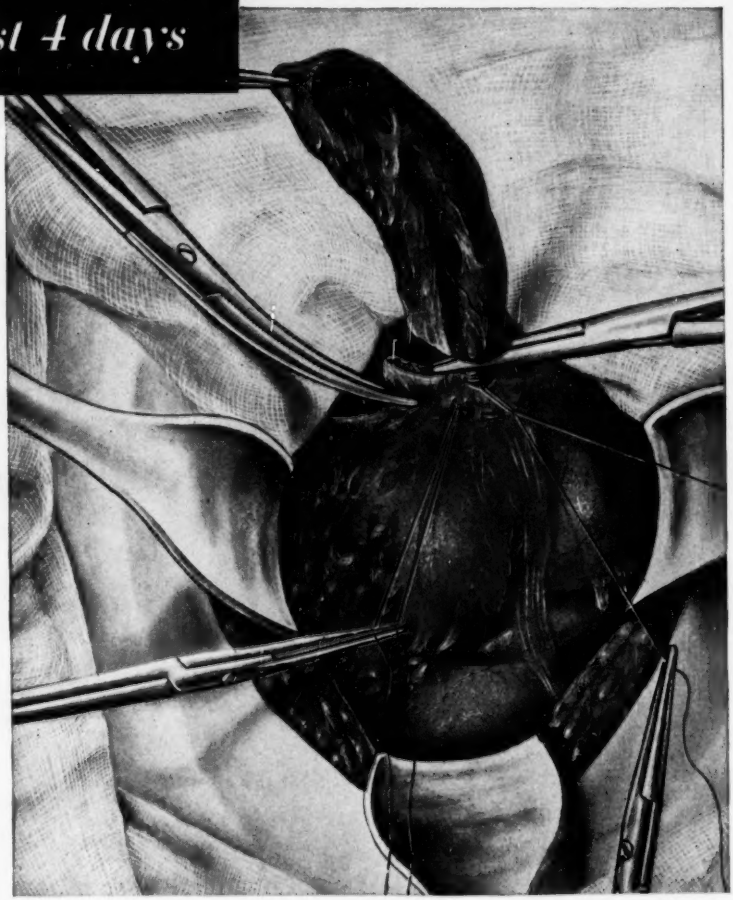

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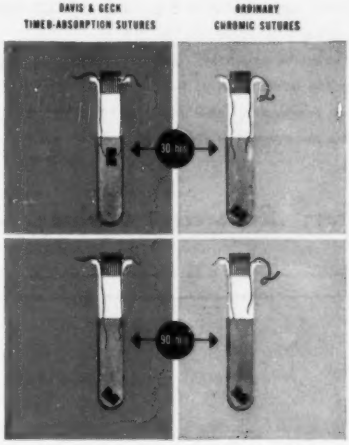

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THE "FEEL" OF THE PATIENT

Presidential Address

J. DEWEY BISGARD, M.D.
OMAHA

IN ALL the history of mankind, no profession has made as much progress and no group of men has contributed as much to human welfare as has the medical profession during this half century. This progress, like most progress, was achieved at a cost, in this case at some sacrifice of the personal relationship between the physician and his patient.

Surgeons of past generations, who were to an extent general practitioners, thought of their patients as persons and cultivated the empathy which is so essential to human understanding. During this period there was no holistic emphasis or discussion of integrative levels. Nevertheless the surgeon had "the feel of the patient" and dealt with him not as another problem but as a feeling person with hopes and ambitions, with disappointments and frustrations, who worked, loved and played.

With the generation preceding the present one came specialization in medicine, and the interests of the surgeon were confined to mechanical problems and those arising for the most part from organic disease. Also at this time came a period of emphasis on science, and surgeons became clinical physiologists and biochemists and translated pathology into abnormal physiology and chemistry. In this approach to disease, which attempts to resolve life into a series of chemical reactions, the psychogenic factors in disease received little consideration. Surgeons indoctrinated with this attitude are inclined to exclude unwittingly the influence of the emotions and the role of the higher levels of adaptive mechanism in their clinical evaluations and to make of the patient a decerebrate preparation which gets about on its brain stem.

The need to structuralize all symptoms of dysfunction may be attributed to the fact that in the course of surgical training emphasis is placed on structures and functions of organs and systems of organs. Man is cut into too many pieces, and the pieces do not fit together. Science in its search for truth rigidly denies the influence of the emotions,

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

so the thinking in applied science unavoidably reflects some of this fundamental discipline. Interest in human behavior has been put so far aside in our medical education that we do not recognize with any distinction in our culture the informed individual referred to in German as a *"Menschenkenner."*

However, we are beginning to understand again the admonishment of Spencer that "science is for life, not life for science" and to realize that the knowledge of man which we had before our medical education began is still important. We cannot parenthetically exclude love, hate, resentment, anger, ambition, aggression and moods in the evaluation of the patient. The artist, the writer and the old family doctor have an intuitive understanding of human beings which they usually express in a more acceptable way than the psychiatrist, whose knowledge is more formal and often put in tonsil-rasping word symbols of Greek derivation.

No one has a greater need to know "the feel of the patient" than the surgeon because no one is given a freer hand in dealing with the lives of others. It is not often that the surgeon's judgment is questioned, and in the operating room it is absolute, for under anesthesia there is no minority report. So important is the surgeon's judgment that it might be well to examine it. His judgment is the product not only of his intellect, his training and his experience but also of his personality makeup, his emotions and at times his identification with one of his preceptors. In way of illustration, it may be pointed out that the judgment of an individual surgeon may be radical or conservative, depending on a number of factors such as his need for approval or on the degree of aggressiveness and self confidence that he possesses. Furthermore, his judgment may change from time to time as his self confidence is shaken or enhanced by personal fortuitous experiences.

Important as these personal influences are, we are concerned with the extent to which the surgeon's judgment is influenced by the feelings of his patients. Does the surgeon consider organs expendable solely in relation to the dispensability of their essential functions? Or does it matter that patients have rather profound feeling about certain organs and their functions and that the loss of these organs may result in difficult personal and emotional adjustments? Is it not well to be aware that mastectomy may be regarded by the patient as a mutilating experience and hysterectomy as a castrating one? Only unawareness of this fact justifies the judgment of the surgeon who removes a sterile but otherwise normal uterus from a young woman for no more reason than that its child-bearing function has been lost. Menstruation may be a "curse," but it is a gratifying one. That this function is symbolic to women of their femininity and fertility does not have the meaning to the

surgeon that it has to the psychiatrist, whose lot it is to deal with some of the emotional problems that arise when this function has been terminated.

Every surgeon appreciates the profound emotional disturbance which results from the loss of an extremity and the personal adjustment that must be made to that loss. Yet many arms and legs have been removed in the treatment of sarcoma of bone, in spite of the lack of evidence that amputation has ever cured a bone sarcoma which would not have been cured by local resection. Also, there is the serious question of the accuracy of a diagnosis of malignancy for certain tumors of bone, judged solely from a biopsy, and the risk of sacrificing an extremity for a benign lesion. For these reasons, the surgeon who is fully aware of "the feel of his patients" will find no justification for amputation in the treatment of bone tumors except for palliation.

In a surgical experience the personal and emotional factors and their influences are most commonly encountered in problems of the gastrointestinal tract, and these are among the most difficult to evaluate. Because ingestion and elimination are vital functions, the gastrointestinal tract becomes a repository of anxiety and of psychopathologic preoccupation. In fact, after birth man's first orientation to the world is in terms of this tract, and from that time on strong emotional feelings are reflected in dysfunction of the digestive system. With this dysfunction comes the distress of somatic expression. It is a rather universal experience that anxiety is expressed by discomfort described in such terms as, "it gave me a sinking feeling in the pit of my stomach" and "my stomach was tied up in knots." This conscious linking of somatic expressions to the emotions is lost at times of conflict. The emotional factor is repressed, and the patient is aware only of the digestive distress. Such complaints as gas and gas pains, a sour stomach and biliousness are common expressions of visceral dysfunction due to emotional problems. Symptoms of this type are referred to the liver by the English. In this country suspicion is often directed to the gallbladder. Every surgeon knows the unhappy results from cholecystectomy in the noncalculus, noncolic group of cases. Several follow-up studies, including one of my own, show that operation in this group fails to relieve symptoms in about 40 per cent of cases. Too often these failures have been attributed to adhesions, duct stasis, residual hepatitis and pancreatitis and dyskinesia and duodenitis. Seldom is there any thought of investigating the probable emotional source of the symptoms, not only before operation but even after it has failed.

In contrast to this record of surgery of the gallbladder, operations which succeed in permanently eradicating peptic ulcers usually bring about relief of symptoms, and yet the theory of psychogenic factors in peptic ulcer has always been acceptable. This is so because the direct

observations of Beaumont on the exposed stomach of Alexis St. Martin and the more controlled studies of Wolff on a patient with a partially exteriorized stomach clearly demonstrated the striking response of the stomach to emotional influences and the fact that these responses in certain circumstances produced ulcerations of the mucosa. No matter what the exciting factors of peptic ulcer, organic disease in the form of ulceration exists and may produce irreversible changes and complications which can be relieved only by surgical intervention. The surgeon should be mindful of the fact that his operation, gastric resection or vagotomy, does not remove the psychogenic factors. The patients still have their emotional problems. The operation, by altering gastric physiology, gives protection from these emotional influences, and the individual patient's adaptive efforts in stress are made easier by the relief from pain and other symptoms of ulcer. The surgeon's responsibility to these patients does not end with the operation; he should see to it, so far as possible, that the problems on the psychophysiologic level also are competently dealt with. In a few clinics, including the University of Nebraska Hospital, an effort is being made to meet this need by assigning psychiatrists to duty in surgical wards. The value of this experiment is yet to be determined. This does not mean that "the feel of the patient" belongs solely in the province of the psychiatrist. The surgeon should learn that the information which he gets from seeing how the patient meets the tests of life may be as important as that obtained in the laboratory from test tubes and burets.

One could dwell at some length on other surgical diseases in which the emotions probably play a considerable etiologic role, such as hyperthyroidism and hypertension. There is also that large group of patients with strictly psychogenic functional disorders which give rise to clinical manifestations that are similar and often identical to those produced by organic disease. Among these are certain neurotic persons who welcome an opportunity to sacrifice a part of their bodies to appease a deeper self-punitive need. This is the background for what has been called polysurgical addiction, and the surgeon recognizing this perversion in the masochist may be spared the experience of leaving a scar to mark the site of another sacrificial offering. However, it must be pointed out that the psychoneurotic person may also have organic disease and that there is always danger that the functional overlay may obscure the organic lesion. This fact was rather well illustrated by a patient who returned to the hospital with extensive pulmonary metastatic carcinoma two months after he had been dismissed with a diagnosis of psychoneurosis. The admitting intern, a rather facetious fellow, readmitted the patient with a diagnosis of "psychoneurosis with metastases." This is another example that the dichotomy of either/or, that is, either organic disease or functional disease, is an outmoded and dangerous concept.

The surgeon, contrary to some opinion, should never become so impersonal that he fails to appreciate the emotional impact on his patient of a surgical diagnosis and a decision to operate. Every operation is a threat to security and accepted by the patient only after repressing his anxiety. In submitting to operation, the patient relinquishes the direction of his destiny and regresses to a more passive dependent attitude. Often this is one of the major decisions of his life.

As the time of operation approaches, the patient's anxiety usually increases. Fortunately, surgeons know this, and most patients are spared full awareness of one of the most disturbing parts of the whole surgical experience, the ritual of the operating room. This was described by a patient as a feeling of being shackled in a torture chamber inhabited by masked bandits who had all the accoutrements of the Ku Klux Klan except the fiery cross. It is well to be mindful that a blindfolded patient, dulled with sedation, is likely to place a personal interpretation on the activities and conversation that go on about him in the corridors and rooms of the operating suite. Often both the patient and his family can be spared anxious moments of suspense by words of reassurance or an explanation of events, such as a delay in the operative schedule.

Immediately after operation repressed anxiety emerges to manifest itself in several ways. Besides the affective expression of anxiety, there are somatic repercussions. Air swallowing, the most common one, is probably responsible in part for nausea, vomiting, distention and gas pains. Later, to compensate for the preoperative anxiety, there is a release of a certain amount of exhibitionism. The patient accentuates the hazards of the operation and the narrow escape from death, and his humor, which before operation was a gallows type, becomes unrestrained. The more gifted write books about their experience.

The regressive behavior which manifests itself by dependency increases after operation, and the most important contribution of early ambulation is the breaking up of adhesions which bind down patients with habits of invalidism. To get "back on his feet" is symbolic to the patient of regained command of his destiny.

Again, the surgeon's responsibility does not end with recovery from operation. His surgical craftsmanship should not constitute a straight jacket that prevents participation in the personal, social and economic problems of his patients. He should understand that the medical profession has a social responsibility beyond medical care. Often there are problems, such as anxiety about temporary or permanent disability, financial support of dependents, job replacement and personal adjustments. Medical social service and other social agencies have done an invaluable job in meeting some of these responsibilities. Yet the need for these services was recognized by the profession with the same

reluctance with which it has relinquished a status quo attitude in medical economics and accepted the challenge of an expanding social security movement.

An attempt has been made to point out the need for cultivating what has been termed "the feel of the patient." This quality of understanding may be intuitive or acquired from a knowledge of the way people live. It comes from liking people and from an interest in human relationships, from an awareness of the patient as an individual, the development of confidence and the providing of an opportunity for the patient to reveal himself. It creates a state of empathy which ameliorates the whole surgical experience. "The feel of the patient" may be naive or sophisticated depending on the degree of interest, training and ability; no matter on what level, it is always an enriching and rewarding experience.

PRIMARY CARCINOMA OF THE LIVER

KENNETH E. LEMMER, M.D.
MADISON, WIS.

THIS SURVEY covers a series of 18 cases of primary carcinoma of the liver observed at the State of Wisconsin General Hospital between 1928 and 1950. Fifteen of the cases came to autopsy, and 3 were diagnosed by means of surgical exploration. The 15 cases were among a series of 5,228 necropsies, giving an incidence of 0.28 per cent. Of the 18 patients, 17 are now dead and only 1 is living, eight months after the onset of her symptoms and five months after the resection of a solitary hepatoma. In the 17 fatal cases, the average duration of symptoms from their onset to the death of the patient was seven months; the shortest time was one and a half months and the longest time forty-six months. In 1 case death was obviously due to cirrhosis of the liver and only a small hepatoma was found. The average age was 61 years, with the youngest patient 47 years and the oldest patient 70. There were 11 men and 7 women in this series.

The commonest signs and symptoms present in the 18 cases were weakness, rapid loss of weight, abdominal pain, abdominal distention, ascites, jaundice and a palpable abdominal mass.

The liver function tests were of little value in establishing the diagnosis in these cases, as in all instances in which the reactions were positive there was other evidence of severe hepatic disease. The roentgenogram also failed to aid in the early diagnosis.

Warvi [1] has revised the classification of primary tumors of the liver and includes both benign and malignant tumors. No attempt was made in this series to include benign tumors, although there was some difference of opinion among the pathologists about the malignancy in 1 case reported. There were 11 cases of hepatomas, with cirrhosis of the liver in 7. There were 6 cases of cholangiomas, with cirrhosis in 4, and 1 case of cholangiohepatoma with cirrhosis. This incidence confirms the reports in the literature that hepatomas are more common than

From the Department of Surgery, University of Wisconsin Medical School.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

1. Warvi, W. N.: Primary Neoplasms of the Liver, Arch. Path. **37**:367-382 (June) 1944.

cholangiomas by a 3:1 ratio.[2] In this group cirrhosis of the liver was present in 10 of the 18 cases.

The incidence of primary carcinoma of the liver, 0.28 per cent, reported here corresponds favorably with that in other reports for the white race published in this country (Hoyne and Kernohan [2] and Strong, Pitts and McPhee [3]). Of particular interest, however, is the high incidence of primary cancer of the liver in the Chinese and in the East African natives. This finding has usually been attributed to a high infestation rate by the liver fluke Clonorchis sinensis or the blood flukes Schistosoma japonicum and Schistosoma mansoni in these areas. There is also a high incidence of cirrhosis of the liver, and tumors of the liver are commonly associated with cirrhosis. It is difficult to determine the part played by parasites in the formation of the cirrhosis as it has been shown by Gilbert and Gillman [4] that in rats fed on a diet similar to that of the African natives frank cirrhosis developed in 20 per cent. The role of chronic irritation in the formation of primary tumors of the liver was pointed out by Tull.[5] A detailed study of certain irritants in the formation of cirrhosis and of tumors of the liver in rats is presented by Rusch and others [6] in their paper on "Experimental Liver Tumors."

Case 1.—Mrs. I. Q., a white woman aged 64, was admitted to the hospital in September 1949, with the chief complaints of a growth in the abdomen. She stated that three months prior to her admission she noticed a mass in the right upper region of the abdomen which had gradually increased in size and caused a feeling of pressure. There were no other symptoms referable to the lesion, but the patient believed that she had lost about 4 pounds (1.8 Kg.) during the past three months. The physical examination revealed the presence of a firm, smooth mass the size of a small grapefruit in the right side of the abdomen. This moved in both directions, descending on respiration, and could not be separated from the liver on palpation. Because of the mobility, it was felt that it might be a cyst of the omentum or of the mesentery. The laboratory studies were noncontributory. The cholecystogram was reported as follows: "The gallbladder has concentrated sufficient dye to be identified and shows some contraction after a fatty meal. It lies over the dome of the mass and has been displaced upward by it. As a result, the mass is seen to occupy space between the gallbladder and the hepatic flexure of the colon." A roentgenogram made after a barium enema was reported as follows: "The colon fills to the cecum without reflux into the ileum. There are no intrinsic defects, and the evacuation

2. Hoyne, R. M., and Kernohan, J. W.: Primary Carcinoma of the Liver, Arch. Int. Med. **79**:532-554 (May) 1947.

3. Strong, G. F.; Pitts, H. H., and McPhee, J. G.: Primary Carcinoma of the Liver, Ann. Int. Med. **30**:791-798 (April) 1949.

4. Gilbert, C., and Gillman, J.: Diet and Disease in the Bantu, Science **99**:398-399 (May) 1944.

5. Tull, J. C.: Primary Carcinoma of the Liver: A Study of 134 Cases, J. Path. & Bact. **35**:557-562 (July) 1932.

6. Rusch, H. P.; Bauman, C. A.; Miller, J. A., and Kline, B. E.: Experimental Liver Tumors, in American Association for the Advancement of Science Research Conference on Cancer, Aug. 3, 1944, Washington, D. C., American Association for the Advancement of Science, 1945, pp. 267-287.

of the enema is good. Directly above the hepatic flexure is a rounded, firm, soft tissue mass about 10 cm. in diameter. This causes moderate downward depression of the hepatic flexure, but the mass does not arise intrinsically in the colon."

Fig. 1 (case 1).—*A*, cholecystogram. The gallbladder has concentrated some dye and lies over the dome of the mass. *B*, roentgenogram made after a barium enema. The hepatic flexure of the colon is depressed by the mass.

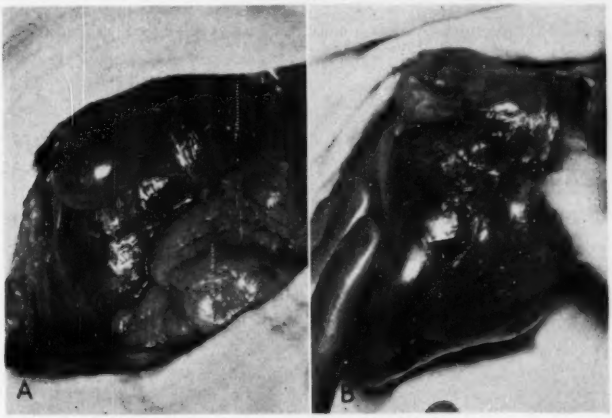

Fig. 2 (case 1).—*A*, the tumor with the gallbladder over the top and with the colon below and medially. *B*, the tumor delivered into the incision.

On the basis of this information it was felt that an exploratory laparotomy was indicated, and this was done on Sept. 8, 1949. Inspection and palpation of the tumor revealed it to be continuous with the right lobe of the liver, with the gallbladder up over the top. The hepatic flexure of the colon was easily separated, as was the omentum. The tumor was freed and found to be somewhat pedunculated, arising

in the right lobe of the liver. A V-shaped resection was done to include normal liver tissue on both aspects. The pathologic report revealed that the specimen was a generous piece of liver (12 by 9 by 8 cm.) with attached gallbladder (8 cm. in length). There was no tumor through the line of surgical amputation of the liver, but there was a large, lobulated, rather friable mass which had replaced most of the normal substance. The cut surface of the tumor, which was firmly lined by connective tissue septums, was mottled light green, dark green and shades of yellow. The gallbladder was grossly unremarkable. The tumor was composed of scattered thin-walled vessels and radiating cords of polyhedral cells. There was a striking resemblance to normal liver, but there was no regular spacing of vessels and there were no portal triads. The nuclei of all tumor cells were larger than normal and were hyperchromic. Pyknotic nuclei were present in small numbers. There were occasional mitotic figures. The diagnosis was hepatoma. The patient had an uneventful postoperative course and was discharged at the end of two weeks.

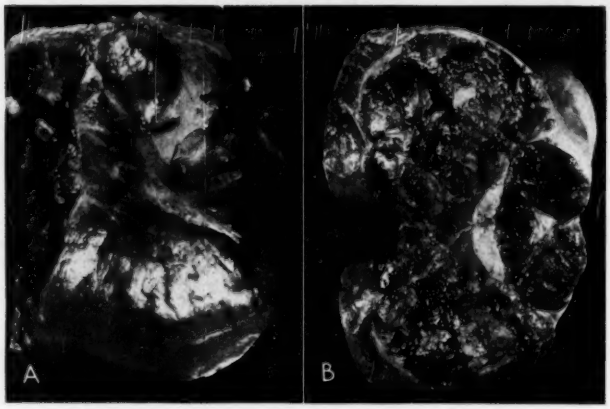

Fig. 3 (case 1).—*A*, the specimen which was removed. *B*, the tumor sectioned. Note normal-appearing liver tissue at left of tumor.

A recent report, five months after operation, revealed that she was well and complained only of occasional constipation. Her weight has been stationary.

CASE 2.—E. J. F., a white man, aged 60, was admitted to the Wisconsin General Hospital on Sept. 6, 1949, with the chief complaint of pain in his neck. He had noticed that he had been tired and weak and had lost 35 pounds (11.3 Kg.) in weight in the past two months. He had noted some distress ten to fifteen minutes after meals but no true pain; otherwise the gastrointestinal history was noncontributory. On physical examination there was some tenderness over the cervical vertebrae. The liver was enlarged 4 fingerbreadths below the right costal margin, and it was firm and nodular. The remainder of the examination revealed no abnormalities. The laboratory studies showed a normal blood cell count. The prothrombin was 100 per cent, and Hanger's test gave a negative reaction. The alkaline phosphatase was 20.2 units. The icterus index was 7 units. The roentgenograms showed degenerative joint disease of the lower cervical and the lumbar regions of the spine

and the lumbosacral joint. A flat plate roentgenogram of the abdomen showed the liver to be enlarged. Metastasis to the chest was not observed. There was some sclerosis of the aorta. A barium swallow showed some varicosities in the esophagus; otherwise it revealed nothing abnormal.

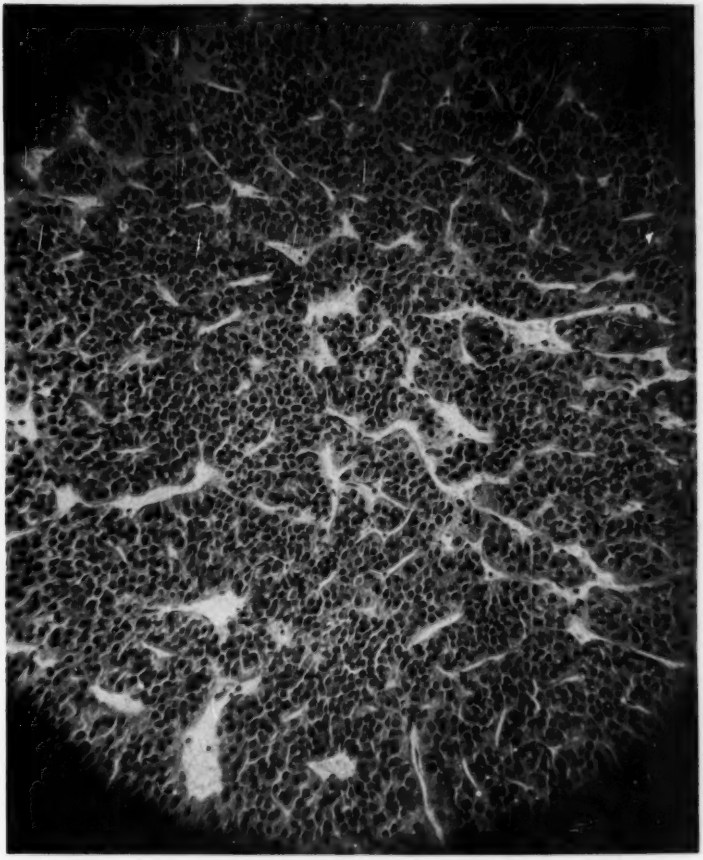

Fig. 4 (case 1).—Photomicrograph (× 170) from a hepatoma without cirrhosis. There are scattered thin-walled vessels and radiating cords of polyhedral cells. There is no regular spacing of vessels, and the portal triads are absent. The nuclei are large and hyperchromatic and show occasional mitotic figures.

On September 15 the abdomen was explored and a large nodular liver was found. There was no other evidence of a malignant growth noted. A biopsy was made of

material taken from the liver, which was reported as follows: "There was striking cirrhosis with chronic inflammation. There were irregular masses of swollen but otherwise unremarkable parenchymatous cells, and there were well outlined nodules composed of moderately atypical cells. The atypical cells which were arranged in

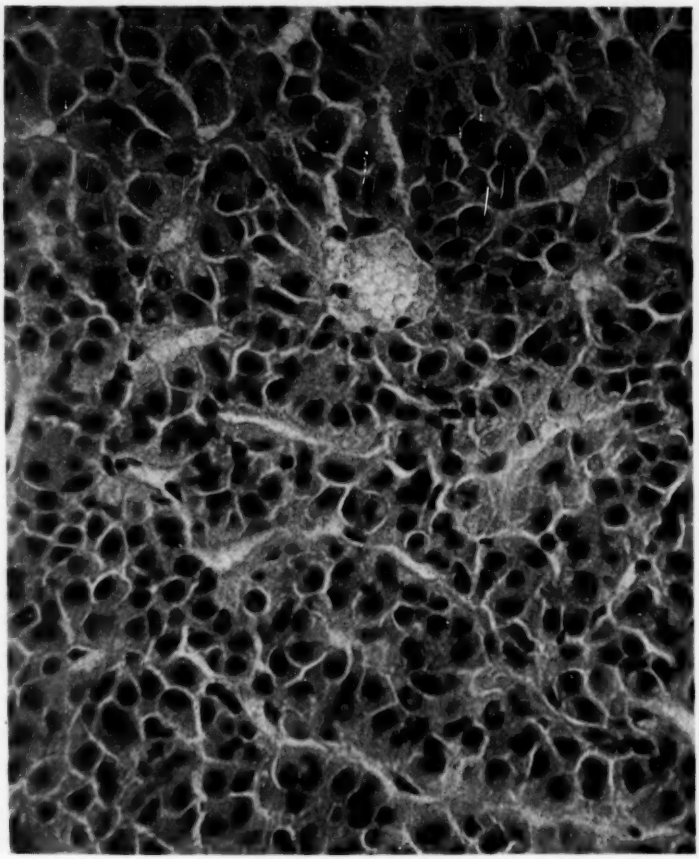

Fig. 5 (case 1).—Photomicrograph (× 900) of a hepatoma showing irregular nuclei with one mitotic figure in the center of the field.

irregular columns had a slightly vacuolated cytoplasm and large prominent nuclei. There were occasional mitotic figures." The diagnosis was hepatoma with cirrhosis of the liver. The patient was discharged on September 22. He returned to his local hospital, where he died in October. Only four months had elapsed from the onset of symptoms until the time of his death.

CASE 3.—G. K. J., a 54 year old white man, was first admitted to the hospital on June 6, 1938, complaining of pain in the right shoulder. The examination of the

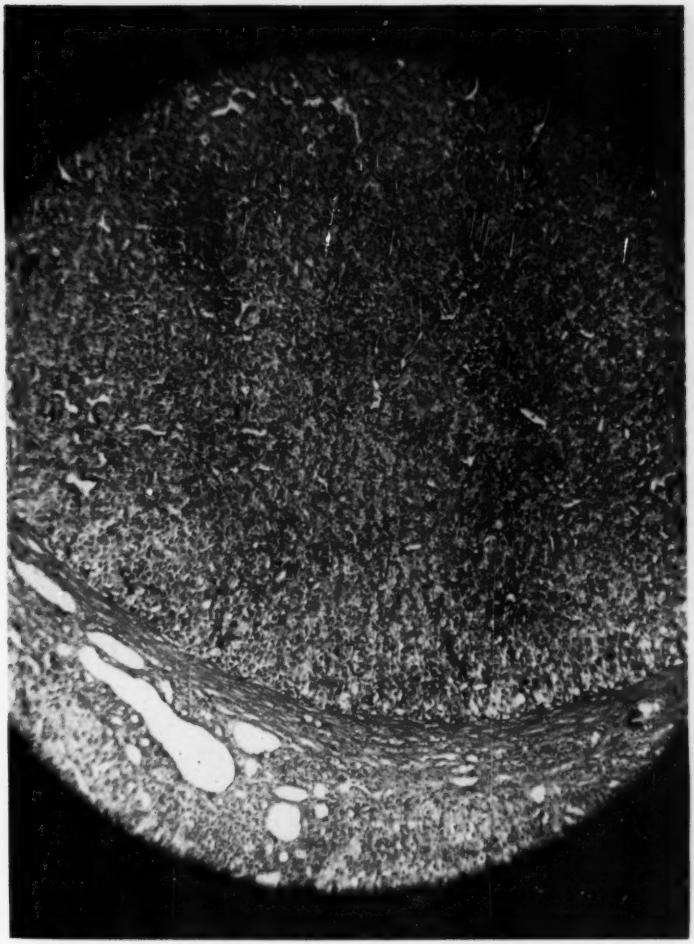

Fig. 6 (case 2).—Photomicrograph (× 80) of a hepatoma with cirrhosis. There is striking cirrhosis, with chronic inflammation. The cells are arranged in irregular columns and have a slightly vacuolated cytoplasm and large prominent nuclei.

abdomen revealed that the liver was palpable 5 cm. below the right costal margin and that there was slight tenderness to percussion over the liver. The laboratory

data were regarded as normal. A roentgenogram of the chest was taken which revealed a clearcut, smooth, rounded mass at the right base. The diagnosis was probable tumor of the pleura involving the diaphragm or a tumor of the liver.

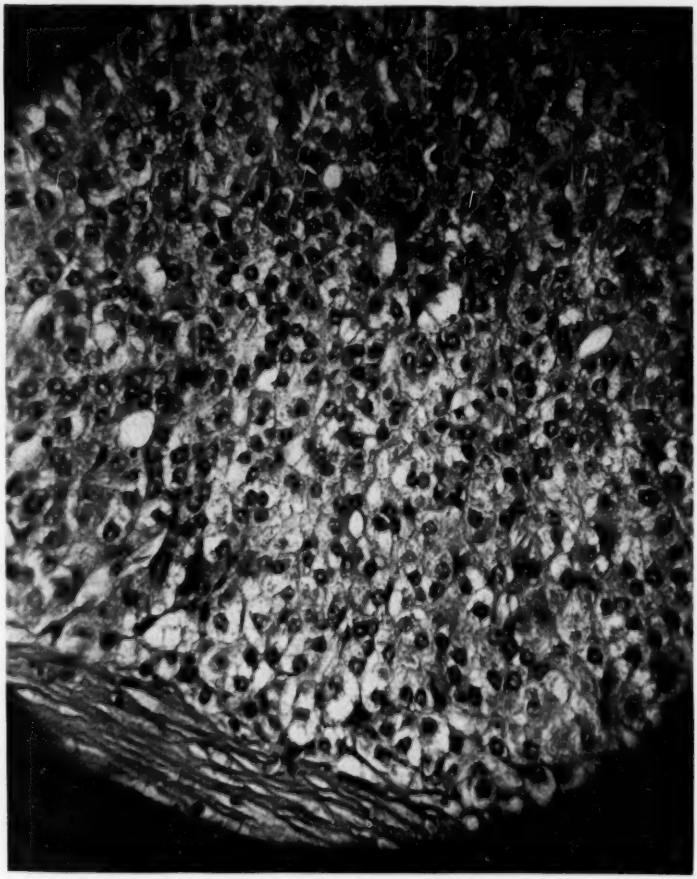

Fig. 7 (case 2).—Photomicrograph (× 330) showing atypical cells with occasional mitotic figures in the nuclei.

At operation a tumor was found lying just medial to the dome of the diaphragm. An incision was made through the diaphragm lateral to the tumor and the tumor separated from the liver, leaving a small bleeding bed which was controlled with two mattress sutures. The mass was removed. The microscopic sections showed a cellular, rapidly growing tumor composed of large closely packed cells. The cells

were associated in some areas with blood-filled spaces and seemed to form these spaces. They had large oval nuclei with considerable hyperchromatism and frequent mitotic figures. There was much necrosis. The capsule was invaded. The diagnosis was angioendothelial sarcoma.[7]

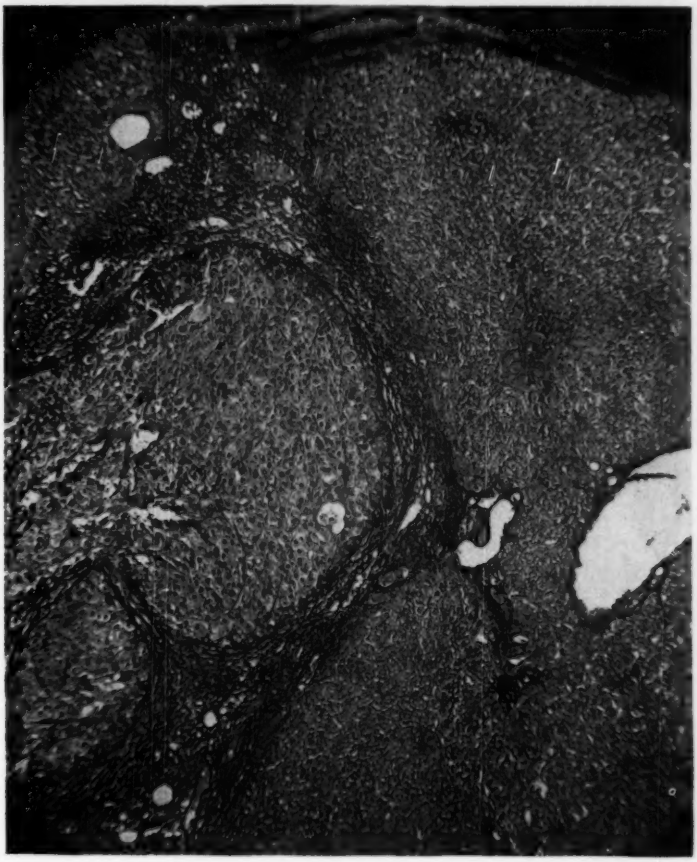

Fig. 8 (case 3).—Photomicrograph (× 90) from a hepatoma, previously diagnosed as a primary endothelial sarcoma of the diaphragm. There is a tumor nodule surrounded by fibrosis, round cell infiltration and areas of uninvolved liver tissue.

7. Gale, J. W., and Edwards, S. R.: Malignant Tumors of the Diaphragm, J. Thoracic Surg. **9**:185-192 (Dec.) 1939.

The patient remained free of symptoms except for some pain in his right shoulder until Dec. 1, 1941, when he began to complain of headaches, gas and belching. At this time the liver was enlarged, tender and nodular, and the cause was considered to be metastasis from the tumor of the diaphragm. He returned in

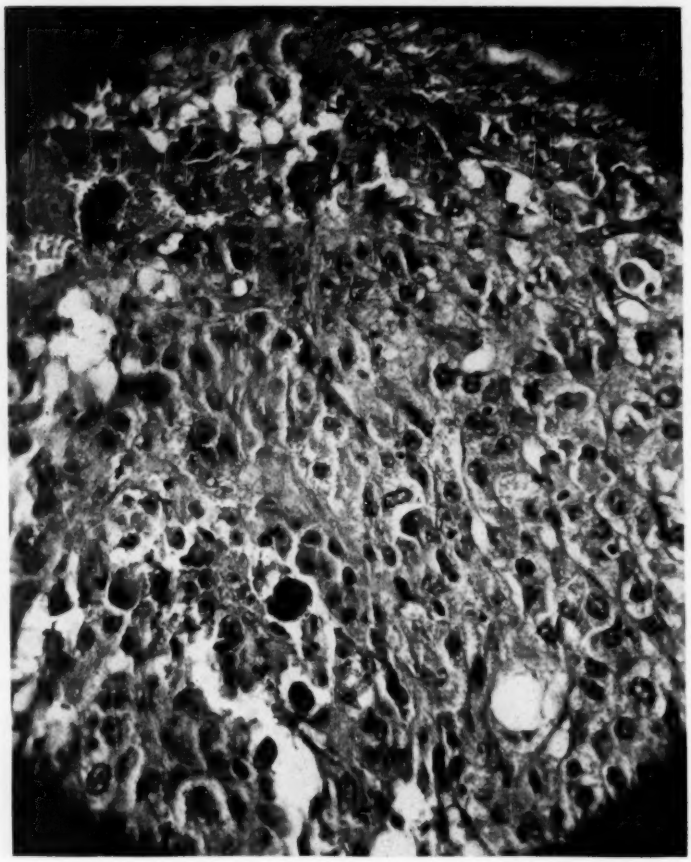

Fig. 9 (case 3).—Photomicrograph (× 330) showing masses of invasive tumor cells arranged in columns. The cells are very large, with granular cytoplasm and oval, pleomorphic, hyperchromatic nuclei containing nucleolei. Mitotic figures are common.

January 1942 with epigastric pain, a palpable mass and fluid in the abdomen. Surgical exploration revealed a large amount of free fluid and an enlarged nodular

liver. There were numerous metastatic glands present around the common duct. A biopsy of the liver showed an invasive tumor composed of masses of cells arranged in columns. The cells were very large, with granular cytoplasm and oval, pleomorphic hyperchromatic nuclei containing nucleoli. Mitotic figures were common. There were areas of liver cells present in which the normal architecture had been destroyed. The cells showed pale granular cytoplasm. There was moderate round cell infiltration. The diagnosis was hepatoma. A review of the sections from the diaphragm at this time indicated that this growth, too, must have arisen from the liver. After this the patient was discharged from the hospital. He died on April 20, 1942.

SUMMARY AND CONCLUSIONS

1. Primary carcinoma of the liver is an uncommon disease in the white race (incidence, 0.28 per cent).

2. It is a disease of older persons (average age, 61 years).

3. The lesion is highly malignant, with an average duration of symptoms of seven months.

4. It is commonly associated with cirrhosis of the liver (55.5 per cent in the present series).

5. Metastasis occurred in one half of the cases (50 per cent).

6. The usual signs and symptoms of intra-abdominal carcinoma were present, and a clinical diagnosis of primary carcinoma of the liver was not made in this series.

SURGICAL SIGNIFICANCE OF SWEAT GLAND LESIONS OF THE BREAST

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AND
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STRUCTURES in the cystic breast composed of cells resembling those of the axillary apocrine sweat glands (hidradenocytes) were noted by several German pathologists.[1] These cells are analogous to the occurrence of intestinal epithelium within the mucosa of the stomach or gallbladder. The peculiar odor of the content of certain cysts of the breast lined by these cells is similar to that of axillary sweat.

DEVELOPMENTAL CONSIDERATIONS

Phylogenetically, the milk glands of mammals are to be regarded as modified sweat glands. The basic structure of the mammary gland is a system of branched ducts, the ramifications of which vary greatly in response to endocrine stimuli. In the resting gland the ducts are lined by a double layer of cells. The blind cords constituting the terminal end pieces are frequently surrounded by stellate-shaped cells which are continuous with the outer layer of cells lining the ducts. These outer cells are collectively referred to as the basket, myoepithelial or stellate cells. The internal secretory layer of the galactophore is clearly contrasted with the external, future myoepithelial layer.[2] The primordial dualism

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Dr. McDonald is from the Division of Surgical Pathology, Mayo Clinic.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

Abridgment of a portion of a thesis submitted by Dr. Watkins to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. (*a*) von Saar, Günther: Ueber Cystadenoma mammae und Mastitis chronica cystica. Arch. f. klin. Chir. **84**:223-279, 1907. (*b*) Krompecher, E.: Zur Histogenese und Morphologie der Cystenmamma (Maladie kystique Reclus, Cystadenoma Schimmelbusch, Mastitis chronica cystica König) des intrakanalikulären Kystadenoms und der Kystadenokarzinome der Brustdrüse, Beitr. z. path. Anat. u. z. allg. Path. **62**:403-472, 1916.

2. Peyron, A.; Corsy, F., and Surmont, J.: Sur la pathologie comparée des tumeurs de la mamelle, Bull. Assoc. franç. l'étude du cancer **15**:21-62 (Jan. 18) 1926.

of the lining of the galactophores has been overlooked by most authors. Although this concept regarding the histogenesis of the external, myoepithelial layer of the adult breast has been little emphasized in this country, it has been useful in explaining many puzzling appearances found in pathologic breast states. The process of secretion in the gland is best observed when it is engaged in its full glandular activity, that is, during pregnancy and lactation. At the beginning of secretion granules appear in the basal portions of the cell and in the vicinity of the nucleus. The papillary-like projections into the lumen are filled with secretion granules. These processes together with a considerable portion of the cytoplasm proper are pinched off to form the secretion, leaving the inner border of the cell with an irregular, fringed appearance.

The breast throughout life exhibits some secretory activity. Except during lactation, the mouths of the ducts are not normally patent, and no secretion can escape. The physiology of the breast entails not merely secretory but also continuous absorptive activity.

APOCRINE AXILLARY SWEAT GLANDS

The apocrine glands occur in such places as the axillas, areola, mons veneris, abdomen, inguinal folds, labia majora and circumanal region (Schiefferdecker [3]). To these glands belong the tasks of producing individual, sexual and racial odors. Morphologically the diagnostic sign of apocrine glands is the formation of secretion by the constricting off of the distal portion of the cell projecting into the lumen. Around the gland tubules is a layer of myoepithelial cells.

The first visible sign of secretion is the supranuclear collection of granules which increase in number progressively with increase in height of the cell. As with the breast, relations exist with the gonads; the first secretion sets in with puberty. During the menopause the axillary glands also undergo involution. The axillary glands in the intermenstruum contain only small resting glands, which in the premenstruum and menstruum swell up to large, profusely secreting glands. Buschke [4] investigated the large axillary apocrine sweat glands in 50 women whose ages ranged from 50 years upward and compared them with those from 10 younger women. In 54 per cent of the persons investigated at the time of the climacteric, marked cyst formation was found, and in 40 per cent the epithelium appeared to be engaged in proliferative processes, corresponding to similar structures in the breast.

3. Schiefferdecker, P.: Die Hautdrüsen des Menschen und der Säugetiere, ihre biologische und rassenanatomische Bedeutung, sowie die Muscularis sexualis, Stuttgart, E. Schweizerbert, 1922.

4. Buschke, Wilhelm: Cystenmamma und Axillarorgan (auf Grund von Untersuchungen an den apokrinen Achselschweissdrüsen in Klimakterium), Arch. f. Gynäk. **152**:418-446, 1933.

CHARACTERISTICS OF APOCRINE SWEAT GLAND EPITHELIUM (HIDRADENOCYTES)

The typical epithelium is composed of high cubocylindric cells two to four times the size of the ordinary mammary alveolar cells, with relatively small round hypochromatic, basally located nuclei and a cell protoplasm which is often irregularly delimited toward the lumen. As signs of apocrine secretion, the free ends are seen to be swollen like the ends of a club, and small protoplasmic spheres are constricted off from the cytoplasm to lie free in the lumen, while in the remaining cells the cytoplasm may be low and have the appearance of the resting stage. Eosinophilic granules or fine vacuoles may be present. Fatty substances in the form of small droplets can be demonstrated with the scarlet red stain; they give positive results when tested for cholesterol and a positive Turnbull's blue reaction. Complete uniformity exists between the structures seen in the breast and the axillary apocrine sweat glands. However, it is not certain that many published papers dealing with atypical or pale epithelium have concerned themselves with the same cell type.

The bright appearance of the so-called pale epithelium is due to the fact that the relatively small, round nucleus diminishes in size in relation to the large cellular cytoplasm, even though the cytoplasm stains darker than in the normal breast lobule. In our study we were interested in obtaining a method of identification of a cell which we regard as highly individual and specialized. General pathologic principles suggest that the presence of clearly defined granules in an epithelial cell indicates that the cell is metabolically active in a specialized capacity. The granules which have been described as acidophilic, siderophilic and fuchsinophilic appear to be the true distinguishing morphologic features of this cell. Askanazy [5] and von Saar [1a] emphasized the eosinophilic granules of the cytoplasm while Schultz emphasized the presence of ferruginous and sudanophilic granules. However, Buschke investigated 12 breasts with the Turnbull blue reaction, and all 12 had numerous areas of eosinophilic epithelium. He found iron only in 2 cases inside the hidradenocytic complexes of such cells. This finding was in contradistinction to the high percentage of positive reactions in the axillary glands. The investigations of Bunting [6] showed the presence of iron irregularly in both the breast and axillary hidradenocytes. Lendrum [7] modified and applied a method originally devised for the granules of the pituitary to the staining of these

5. Askanazy, M.: Die Cysten-Mamma (Morbus Reclus) und ihr latenter Zustand, Schweiz. med. Wchnschr. **55**:1017-1021 (Nov.) 1925.

6. Bunting, Henry: Cytochemical Properties of Apocrine Sweat Glands Normally Present in the Human Mammary Gland, Anat. Rec. **101**:5-12 (May) 1948.

7. Lendrum, A. C.: On the "Pink" Epithelium of the Cystic Breast and the Staining of Its Granules, J. Path. & Bact. **57**:267-270 (April) 1945.

hidradenocytic granules. We attempted to apply his method to paraffin sections prepared with formaldehyde-fixed tissue without obtaining precise results. Our modification of Lendrum's staining method is the subject of another communication.

Fig. 1.—Group of hidradenocytic cysts (von Saar's cysts). These cysts always occur in such groups. Growth activity is demonstrated by papillary foldings. The granules of the cytoplasm stain dark black. (Modified Lendrum stain, × 55.)

To orient ourselves with the results of these tests, we employed a series of 50 sections of typical pale epithelial cysts in typical arrangement

obtained in cases of cystic disease. It must be emphasized that some of the cells in each cyst showed eosinophilic granules, but a larger percentage of the individual cells showed fuchsinophilic granules, and in the large blue-domed cysts where the epithelium was much compressed the Lendrum stain demonstrated granules when the hematoxylin and eosin did not (figs. 1 and 2). Only 1 section showed any iron granules

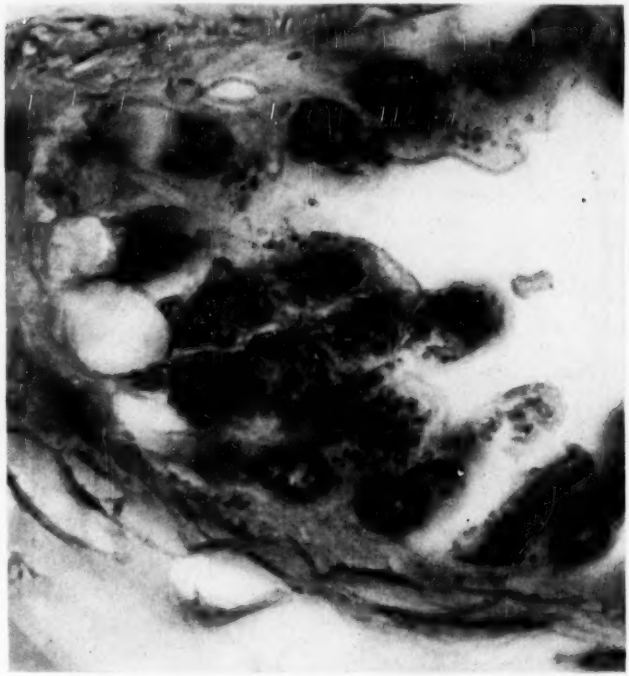

Fig. 2.—Hidradenocytic cyst of the breast. The hidradenocytes are almost filled with fine and large granules, especially in the distal portions of the cells; these distal portions are pinched off to form the secretion. Although the nuclei always appear dark with this stain, the several nucleoli may be easily distinguished. (Modified Lendrum stain, × 1040.)

in the tissue, and these were confined to 3 cells. It was apparent that the Lendrum stain was the most sensitive stain for demonstrating these granules. No other cells of the breast gland gave positive results.

Lendrum had stated that he had always been able to demonstrate fuchsinophilic granules in axillary apocrine sweat glands. All the cells

of the apocrine sweat glands from 15 specimens obtained from the axilla contained eosinophilic and fuchsinophilic granules. Myoepithelial cells were present about each gland tubule and were especially well demonstrated by the modified Lendrum method.

METHODS OF STUDY

In our studies of the breast lesions entire whole breasts were used. The formaldehyde-fixed specimen was serially sectioned into slabs of approximately 4 mm. thickness. This permitted a thorough gross inspection of the organ, and specimens were then selected for microscopic study. Several blocks were taken from each specimen. Each block was fixed and sectioned, then stained with hematoxylin and eosin, by the Berlin blue method and by our modified Lendrum method. Selected specimens were obtained for frozen sectioning and subsequent treatment to demonstrate cholesterol and fat.

CHRONIC CYSTIC MASTITIS

Of 40 whole breasts which were removed because of cystic disease, 38 showed evidences of glandular hyperplasia involving the ordinary mammary alveolar epithelium and 20 showed hyperplasia involving the hidradenocytic epithelium. Twenty-two of 40 breasts contained large cysts that were more than 3 cm. in diameter; in these the nature of the lining epithelium was impossible to determine. Sixteen breasts presented small cysts (less than 3 cm. in diameter) lined by ordinary alveolar epithelium, while every breast in varying degrees showed small hidradenocytic cysts. In 15 breasts there was evidence of ductal ectasia. The histologic features of this lesion differed in no way from the ductal ectasia of comedo mastitis and will be discussed further with that lesion. Multiple papillomas were found in 3 cases. In the 30 blue-domed cysts (of Bloodgood[8]) that were less than 3 cm. in diameter, hidradenocytes were always present (fig. 3); in the 20 cysts larger than this, although the exact nature of the lining cells often could not be determined, smaller hidradenocytic cysts could always be demonstrated in the wall and the surrounding breast tissue.

Besides the characteristic grayish brown color of the fluid obtained from blue-domed cysts, certain constituents have been found to be characteristic. Cholesterol is the substance present in largest amount; it is remembered that it is a specific secretion product of the hidradenocyte.

8. Bloodgood, J. C.: The Blue-Domed Cyst in Chronic Cystic Mastitis: Its Relation to the Cure of Cancer, to Benign Lesions of the Breast, and to the Educational Program, J. A. M. A. **93**:1056-1059 (Oct. 5) 1929.

Dempsey, Bunting and Wislocki [9] always obtained negative results when they applied the Liebermann-Burchard test to the mammary epithelium of the lactating mammary gland. Evidences of hemorrhage or other sources of cholesterol were not present. The hypothesis is attractive that it is the secretory activity of the hidradenocyte which is responsible at least in part for the cholesterol found in this location. The compressed epithelium lining the blue-domed cysts is much more convincingly demonstrated to be composed of hidradenocytes with the Lendrum stain

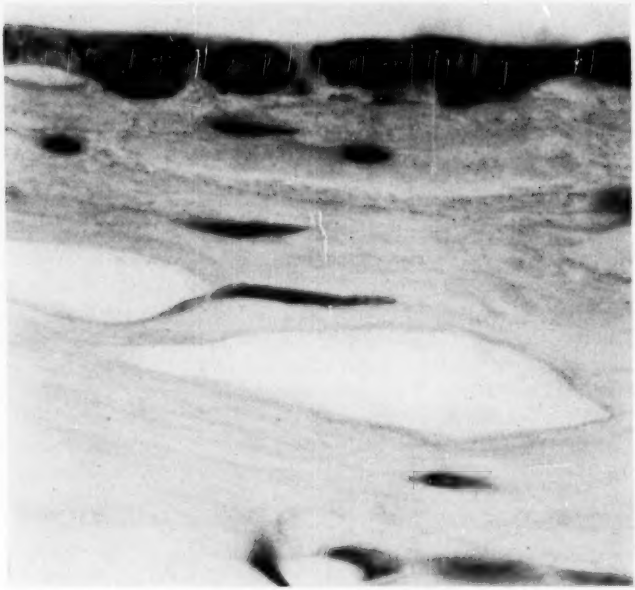

Fig. 3.—Wall of a large, blue-domed cyst 2.5 cm. in diameter. The compressed cells are flattened and can be identified only with special stains. The granules tint faintly and tend to be grouped about the nucleus. The lower portion of the section shows dense fibrous tissue. (Modified Lendrum stain, × 920.)

than with other methods. Glandular hyperplasia involving both the ordinary and hidradenocytic epithelium is a constant feature of the cystic breast, as is the occurrence of the small hidradenocytic cysts. Cysts lined by the ordinary mammary alveolar epithelium occur less frequently, and larger cysts, in general, are less common.

9. Dempsey, E. W.; Bunting, Henry, and Wislocki, G. B.: Observations on the Chemical Cytology of the Mammary Gland, Am. J. Anat. **81**:309-342 (Nov.) 1947.

INTRACANALICULAR PAPILLOMAS

These adenomatoid growths occurring in the glandular spaces of the breast have a definite papillary arrangement and present a stalked appearance. Not included here were lesions described as simple hyperplasia of the duct epithelium or the papillary processes found uniformly within the small hidradenocytic cysts. A majority of the cases of papillomas presented multiple growths that involved several ducts. Two types of papilloma have been recognized: the pure papillary form and the papillary adenomatoid form. Forty-five whole breasts which were the seat of 1 or more papillomas were examined by the method outlined previously. Thirty-six showed multiple papillomas. The commonest epithelial component was the usual ductal type of epithelium which covered most of the papillary processes. This type of epithelium alone formed the sole epithelial component in 27 of the 45 cases. In some areas it appeared to be in the process of apocrine secretion. The hidradenocytic epithelium formed an essential part of the lesion in 18 cases in which it composed up to 50 per cent of the total amount of epithelium. It appeared as pale pink in sections stained with hematoxylin and eosin; the modified Lendrum-stained sections showed definite granules, and usually the cells appeared to be in the process of active secretion (fig. 4). The granules were well defined. In 7 breasts atypical epithelial cells were found.

The commonest of these unusual epithelial types is the pale "clear cell." These cells have clear cytoplasm and present no signs of granules with any of the stains, including the modified Lendrum stain, and no signs of apocrine secretion. They suggest great similarity to the cells of the pars secretoria of the eccrine sweat glands. The nuclei of these cells are large, round, centrally located, poor in chromatin and vesicular, with large bluish-staining nucleoli. The cytoplasm stains pale pink with eosin. In some areas these cells are arranged in tubules with two layers of cells. About the tubules and often scattered in masses throughout the tumor are myoepithelial cells. Small vacuoles present in the cytoplasm may be regarded as evidences of secretory activities.

An uncommon type of epithelium which is encountered occasionally in papillomas is a pale-staining cell which has a vacuolated cytoplasm, clear cell limits and a centrally lying, dark nucleus. It resembles somewhat the cells of the sebaceous glands. Scarlet red stains some lipid droplets in their cytoplasm. The modified Lendrum stain gives negative results; there is no indication of any granules of any type. The cells do not contain iron pigment.

The last group of cells that are of interest consists of narrow, long spindle elements whose protoplasm can branch in stellate fashion and

join with other cells to form a syncytium. The origin and nature of these cells have been debated, but they conform to that cell which has been termed the myoepithelial cell. The cytoplasm of these cells stains dark red in hematoxylin and eosin preparations. The nuclei are rodformed

Fig. 4.—Intraductal papilloma. The epithelial cells covering the connective tissue stalk are of the usual ductal-acinar type (right lower) or of the hidradenocytic type (left) with numerous black granules. The cellular promontory (upper left) shows 2 acini lined by clear cells without granules or signs of apocrine secretion; they resemble the pars secretoria of the eccrine sweat glands. Attached to the right side of these acini is an area of hidradenocytes with prominent granules. Beneath the epithelial cells throughout are scattered fusiform, dark-staining nuclei which represent myoepithelial cells. (Modified Lendrum stain, × 264.)

and rich in chromatin. On cross section they appear cubical or triangular. With the Lendrum stain these elements are seen to possess striations which closely resemble those seen in smooth muscle fibers.

These interesting myoepithelial cells are essential components of the tumor and, in our series, could be demonstrated in every breast that contained papillomas, the frequency varying from papilloma to papilloma. They are found throughout the tumor, in the villous and in the more adenomatous portions. They are situated externally to the ordinary epithelium, to the hidradenocytes and to the clear cells. In some areas they nicely surround the tubules formed by the clear cells. Elsewhere they may form compact masses which closely resemble those seen in the canine mixed tumors of the breast. When they form the chief component of the papilloma, they are said to be papillomas of the "transitional cell type" (Saphir and Parker [10]) or "adenocarcinoma" (McDonald [11]).

The stroma of the papilloma is in general not unusual. The loose connective tissue core contains several delicate blood vessels and few cells typical of chronic inflammation. In the papillomas of 18 breasts in our series greater or less degrees of infarction were present. This process is followed by organization, hyalinization and connective tissue replacement of the tumor.

In the past the presence of a brownish discharge from the nipple has always been interpreted as due largely to the consequences of infarction. The pigment was believed to be of hematogenous origin. However, discharge from the nipple was the presenting symptom in all our cases, yet in less than one fourth could erythrocytes or blood pigment be demonstrated in the discharge from the nipple. It appears that the factor of secretion has been largely ignored in determining the site of origin of the discharge. The active apocrine secretion of the hidradenocytes contributes without a doubt to the total mass of secretion. The secretion of the ordinary alveolar epithelium also contributes to this product. The granules of secretion from the hidradenocytes can be traced from the process of extrusion from the cell into the ducts and in the secretion from the lactiferous ducts.

Six breasts showed 1 or more large cysts, the exact nature of the lining of which could not be accurately determined. The smaller cysts (less than 3 cm. in diameter) provided more interesting findings. Four breasts contained small cysts lined with the ordinary alveolar epithelium. However, 41 of the breasts that contained papillomas also contained small cysts lined by hidradenocytic epithelium. The number of cysts

10. Saphir, Otto, and Parker, M. L.: Intracystic Papilloma of the Breast, Am. J. Path. **16**:189-210 (March) 1940.

11. McDonald, J. R.: Apocrine Sweat Gland Carcinoma of the Vulva, Am. J. Clin. Path. **11**:890-897 (Dec.) 1941.

in any given breast varied considerably, as did the size of the cysts. Hand in hand with the finding of these small hidradenocytic cysts was the finding of glandular hyperplasia involving these same elements. Forty-two breasts showed this hyperplasia. Nineteen showed glandular hyperplasia involving the ordinary alveolar epithelium.

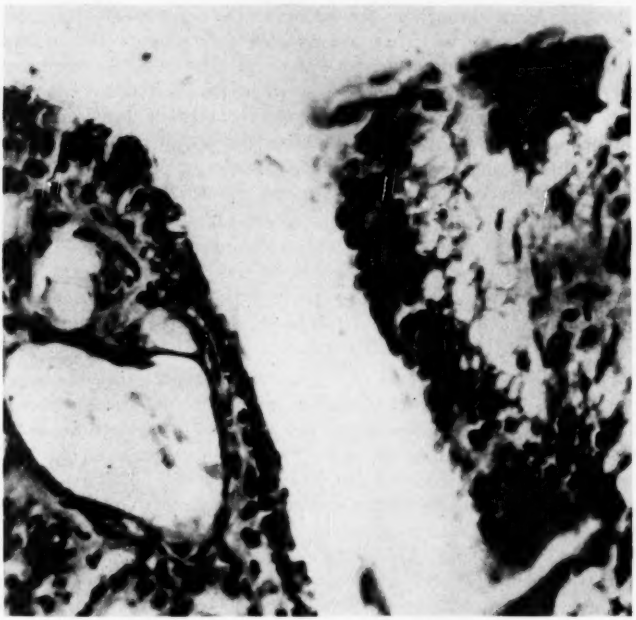

Fig. 5.—Hidradenoma of the vulva. To the left is a portion of the tumor covered by low columnar epithelium which resembles that of the ducts of the breast; its nuclei are dark-staining and clublike in form, and the cytoplasm is scanty and contains no granules. Below this epithelium the tumor is composed of several tubules lined by low cuboidal epithelium which resembles that of the eccrine sweat glands. Their nuclei are spherical and dense; the cytoplasm is clear and contains no granules. The papillary process to the right is covered by typical hidradenoid cells. The granules are darkly stained and appear in the distal portion of the cells. Below the epithelium is a loose stroma; in this are long, hyperchromatic nuclei which represent myoepithelial nuclei. (Modified Lendrum stain, × 265.)

HIDRADENOMAS OF THE SKIN

Ten hidradenomas, 9 from the vulva and 1 from the anus, in the group previously studied by McDonald were reviewed. Up to 30 per cent of the epithelium of this tumor may be of the hidradenocytic type, identical to that seen in the axillary apocrine sweat glands and in the

breast lesions. With hematoxylin and eosin staining the epithelium in our series was always pale pink, but definite granules were demonstrated by means of the modified Lendrum stain. None of these cells gave a positive reaction with stains for iron. Interestingly, iron has never been demonstrated in the hidradenocytes of the vulva, anus or abdominal wall. The hidradenocytic epithelium was seen to be usually engaged in active secretion (fig. 5).

In 2 cases a third type of epithelium was found. The cells were large and clear, with a foamy type of cytoplasm which reminded us of the cells of a sebaceous gland. Scattered throughout 5 tumors were small-lumened tubules lined by a low cuboidal epithelium which resembled that of the secretory portions of the eccrine sweat glands. The nuclei were spherical and dense; the cytoplasm was clear and contained no granules.

The most frequent type of epithelial element in these tumors was a cell which resembled those lining the ducts of the breast. The cytoplasm was scanty and contained no granules. A prominent component of 8 of these tumors was the typical myoepithelial cell.

A comparison of the histologic elementary composition of intraductal papilloma and hidradenoma shows complete correspondence of their structures. They are both benign tumors. Certain statements made in the past relative to "low grade" malignancy were based essentially on failure to identify the cellular components of the tumors and to regard unusual cell forms as "dedifferentiation." We have never seen a malignant lesion which reproduced the structure of either of these two types of tumor.

COMEDO MASTITIS

The essential lesion of comedo mastitis is a diffuse cystic dilatation of the milk ducts not secondary to ductal obstruction. Bloodgood [12] described a clinical picture of breasts with dilated ducts beneath the nipple—the varicocele tumor of the breast. The ducts, large and small, were dilated, with distinct smooth walls and contained brown, green, milky or creamlike material of various degrees of viscosity and consistency. He noted that the condition is frequently associated with discharge from the nipple. The ectatic ducts are filled with fluid or grumous material. In a majority of cases the material filling the ducts is thick, grumous and pasty.

The epithelium lining these ducts is of the usual mammary type. Stratification of the epithelium never occurs, although at some areas the epithelial cells may be missing entirely and fat-laden phagocytes may

12. Bloodgood, J. C.: The Clinical Picture of Dilated Ducts Beneath the Nipple Frequently to be Palpated as a Doughy Worm-Like Mass—the Varicocele Tumor of the Breast, Surg., Gynec. & Obst. **36**:486-495 (April) 1923.

project into the ducts giving the impression of stratified epithelium. Flattening of the epithelium and apparent metaplasia to a squamous type occur.

As we have emphasized, the breast is a continuously secreting organ. The essential feature of comedo mastitis seems to be an anomaly of the balance between secretion and absorption. It is apparent that in the normal, nonlactating breast, the process of absorption of secretion balances that of formation of secretion. This lesion, therefore, could result from an increase of production of secretion over the ability of the normal capacity for absorption or from a decrease of ability of absorption in relation to a normal amount of secretion. These features, however, would be modified by any change in the chemical composition of the secretion itself. Without doubt, desquamation of the epithelium occurs, and the epithelial debris contributes to the content of the duct. There is little evidence that the character of the secretion itself is changed.

Since the alveoli themselves in this condition are unaffected, the fault would appear to lie in the ductal system, that is, the main disturbance is one of absorption of normal secretion. Stasis of this material in the ducts produces pressure atrophy of the lining epithelium, so that in some places it may be lacking completely. In many sites the periductal connective tissue shows marked fibrosis and infiltration by cells typical of chronic inflammation. In sites where secretion has gained entrance to the periductal tissue and the breast stroma, evidences of inflammation occur, especially if the penetration is into fatty tissue. These sites often show evidence of subacute purulent inflammation or even abscess formation—a lesion which has been called "plasma-cell mastitis." This lesion is in harmony with others provoked by the entrance of difficultly metabolizable lipid substances into the tissue spaces. Foote and Stewart [13] concluded that this lesion, comprising the features of ductal stasis, ductal dilatation and periductal mastitis, was not related to the lesion complex dominated by proliferative and cystic lesions. However, in our cases glandular hyperplasia was a rather frequent finding.

Besides the lesion involving the larger ducts, there is another lesion which has never been recognized as an entity. Clinically, each of these breasts has been thought to be the seat of a papilloma because of discharge from the nipple. In our cases this discharge was never grumous or thick but rather a thin, watery discharge of a grayish brown color often resembling the discharge seen from an infarcted papilloma. On section the breasts showed dilatation of ductal structures beneath the nipples and extending throughout the parenchyma. The ducts, although

13. Foote, F. W., and Stewart, F. W.: Comparative Studies of Cancerous Versus Noncancerous Breasts, Ann. Surg. **121**:6-53; 197-222 (Jan.) 1945.

dilated, were never thick-walled and were always filled by thin, watery fluid which was grayish brown.

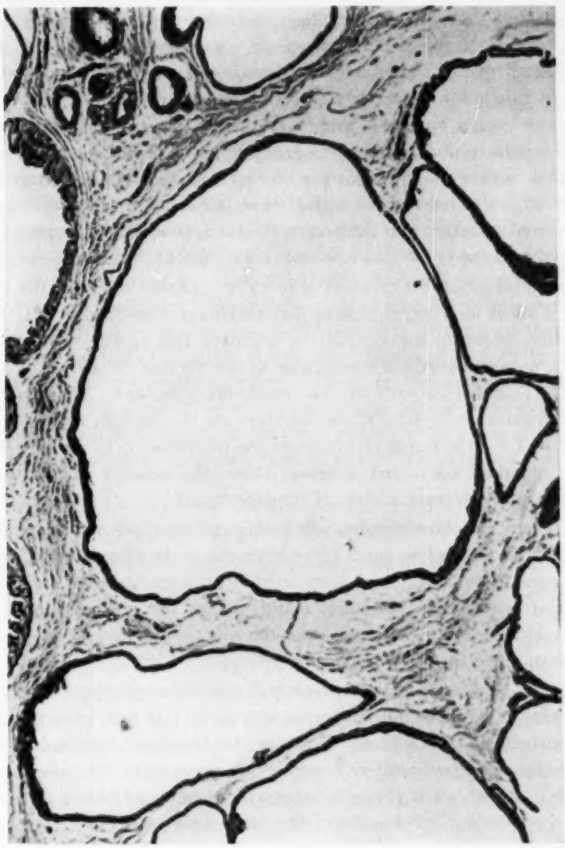

Fig. 6.—Comedo mastitis of the hidradenocytic type. Low power view of dilated ducts lying just below the nipple; originally they were filled with typical thin, grayish brown fluid. The hidradenocytes lining the ducts are seen to be rather dark staining even at this power. Note the more usual-appearing hidradenocytic cysts at the left of the figure.

Microscopically the dilated ductal structures presented an unusual appearance. The cells lining these ducts were all of the hidradenocytic type, most of them in the process of active secretion (fig. 6). We have

called this lesion "comedo mastitis of the hidradenocytic type." Without exception these lesions have been diagnosed clinically as intracanalicular papillomas. Loeschke made wax reconstructions of cystic breasts and demonstrated that the eosinophilic cysts originate from the secretory end apparatus of the milk lobule; their excretory ducts parallel those of the small gland lobules and both may empty into the same central duct. In this lesion, however, the ectatic ducts lined by hidradenocytic epithelium do not appear to empty into ordinary central ducts, or else these ducts have undergone hidradenocytic transformation. There is no indication in other lesions that the central ducts undergo this transformation, so one is led to believe that these structures proceed to develop in the usual manner from the secretory end apparatus and hypertrophy so that they come to overshadow and replace the usual breast structures.

The explanation for this lesion is more apparent than for the same lesion of stasis affecting the gland parenchyma proper, lined by the usual epithelium (comedo mastitis of the ordinary type). The cells of this lesion are more overtly demonstrable in the process of active apocrine secretion than are the ordinary mammary epithelial cells. The abnormal cell aggregates engaged in active secretion are the obvious source of this secretion. Thus the lesion results from the proliferation of the hidradenocytes and their continued secretion above the capacity to absorb the secretion; it represents a state of hypersecretion.

Forty breasts showing comedo mastitis of both types were examined. In 26 of the 40 breasts small hidradenocytic cysts were present, while only 4 breasts contained small cysts lined by ordinary alveolar epithelium. Glandular hyperplasia involving epithelium of the ordinary type was present in 27 breasts; hyperplasia of the hidradenocytic epithelium was present in 25 of the 40 breasts.

The last-mentioned lesions, which are regarded as proliferative lesions, have been stated to be rather uncommon in breasts that are the site of the obstructive, stasis lesions. However, the findings described emphasize the fact that proliferative processes do accompany the main lesions of comedo mastitis, and altered relations of secretion and absorption may be another mode of expression of the proliferative tendency.

COMEDO CARCINOMA AND PAGET'S DISEASE

Comedo carcinoma, or comedo adenoma as Bloodgood termed it, has been the subject of debate regarding whether or not it is truly malignant. To us comedo carcinoma represents an intraductal carcinoma in situ which may or may not be accompanied with an infiltrating, interstitial growth. This lesion bears an intimate relation to so-called Paget's disease of the nipple. In our laboratory we have contended that Paget's disease

represents an in situ squamous cell epithelioma of the skin of the nipple always associated with an underlying intraductal carcinoma of the breast parenchyma. In about 50 per cent of our cases the carcinoma had ceased to be entirely intraductal and had invaded the basement membrane, to produce an ordinary infiltrating carcinoma of the breast.

Fifty breasts which were the site of comedo carcinoma were examined. In 47 of the 50, extraductal extensions of the carcinoma, as well as the constantly occurring intraductal portion, were present. Although the cells associated with this lesion had previously been described as "large pale cells," "cellules claires" and so forth, we never obtained any evidence that they were derived from hidradenocytic epithelium. To be sure, the cells were clear, that is, their cytoplasm was clear and devoid of specialized inclusions no matter what stain was employed to study them. The modified Lendrum stain was always without any positive result. In 7 such breasts there was an associated squamous cell epithelioma in situ of the nipple. The objection will be raised that with the loss of specialized function which accompanies malignant transformation of a cell one could not expect to find the fuchsinophilic granules in these cells. However, these cells were in large part those of carcinoma in situ, and such cells in similar situations elsewhere continue to produce their specific secretory products, such as mucus and keratin.

OCCURRENCE OF HIDRADENOTIC EPITHELIUM IN MALIGNANT TUMORS

The delimitation of sweat gland cancers from other similar-appearing cancerous tumors is difficult because only those cancers can be regarded as sweat gland cancers which show recognizable histologic signs of normal sweat glands. Krompecher [1b] emphasized that the cystic apocrine sweat gland tissue of the breast is frequently the source of malignant tumors; however, he stated that "a direct transition of the pale epithelium lining the cysts into that of the cancer nests is not provable." Lee, Pack and Scharnagel [14] indicated that no less than 25 per cent of all cancers of the breast are of the sweat gland type. They emphasized as distinctive signs the eosinophilia of the cytoplasm and the occurrence of pale epithelial cells and myoepithelial cells. Willer [15] has reported 2 cases which he considered as examples of apocrine cell carcinoma of the breast. However, no characteristic identifying signs of the cells were presented.

There is another type of tumor which was of interest, and that is the so-called cystic carcinoma. Since the hidradenocyte plays such an impor-

14. Lee, B. J.; Pack, G. T., and Scharnagel, Isabel: Sweat Gland Cancer of the Breast, Surg., Gynec. & Obst. **56**:975-996 (June) 1933.

15. Willer, H.: Ueber die apokrinen Drüsen und den Krebs der weiblichen Milchdrüse, Zentralbl. f. allg. Path. u. path. Anat. **70**:49-55 (May 30) 1938.

tant part in the genesis of breast cysts, it was thought pertinent to investigate the so-called cystic carcinomas. There are three conceivable ways in which a cyst may be associated with a carcinoma. The cyst may arise through central necrosis or through the secretory activity of the cancerous epithelium, or the carcinoma may arise in a preexisting cyst. Despite prolonged search we have found examples of only the first method of origin. The notable tendency of the hidradenocyte to form papillae in the small cysts suggested that if any papillary carcinomas of the breast existed they might be composed in part at least of hidradenocytes. Again, we have been unable to find an example of a papillary adenocarcinoma of the breast which was malignant and metastasized to lymph nodes but preserved its papillary structure—in other words, a tumor similar to the papillary adenocarcinoma of the thyroid. In the

TABLE 1.—*Differential Features of Intraductal Papilloma and Intraductal Carcinoma*

Feature	Intraductal Papilloma	Intraductal Carcinoma
Cells	Polarity preserved	Polarity lost
Nuclear differences	Slight; actually exist only among hidradenocytes	Marked
Mitotic figures	Regular and few	Nuclear dissimilarity, hyperchromatism, pathologic mitotic figures, amitotic division, prominent nucleoli
Architecture	Adenomatoid; carefully formed glandular spaces with preservation of papillary stroma	Concentric layering of cells, often with central necrosis
Hidradenocytes	An integral part	Never been identified
Myoepithelial cells	An integral part	Never occur

literature the so-called papillary carcinomas were usually ordinary carcinomas that invaded sites which contained hidradenocytic cysts. Often the term "papillary" was entirely misleading, and the growth was a solid carcinoma.

We studied 40 breasts that were the site of nodular adenocarcinoma. In none of the cases did the cells of the carcinoma resemble the hidradenocytic cells. Although in general many of the cells were pale and eosinophilic, none contained any eosinophilic or fuchsinophilic granules. There were no transition forms which could be identified in our sections. Whenever malignant tissue appeared to be surrounding a hidradenocytic cyst, that cyst preserved its myoepithelial covering and appeared to be engulfed by the carcinoma rather than contributing any element to it.

Thus, we found no basis for the idea of a "sweat gland carcinoma" of the breast or for a papillary adenocarcinoma of the breast. The so-called cases of malignant intraductal papillomas are in reality cases of intraductal carcinomas; the differential features are summarized in table 1.

DEVELOPMENT OF THE HIDRADENOCYTE IN THE APPARENTLY NORMAL BREAST

Of 200 breasts from 100 women who were more than 40 years of age, 65 per cent showed cysts lined with hidradenocytic epithelium (Borchardt and Jaffé [16]). Korpassy studied 600 breasts from 300 female bodies; the causes of death were not related to the breasts or to the puerperium. Of these 300 cases, hidradenocytic cysts were present in 115 (38.3 per cent). Also, pale epithelial cysts were found to occur more and more frequently with increasing age. Berning and Bücker [17] examined 50 breasts and could demonstrate structures resembling axillary apocrine sweat glands in 42. They compared the occurrence of apocrine sweat gland cysts in the breast to the heterotopic islands of gastric mucosa in the esophagus which Schridde had demonstrated in 70 per cent of all men. They regarded the concept of metaplasia as incor-

TABLE 2.—*Incidence of Apocrine Epithelium as Reported by Foote and Stewart*

Age, Yr.	Incidence of Apocrine Epithelium in	
	Noncancerous Breasts, %	Cancerous Breasts, %
30-40	33	25
40-50	47	44
50-60	40	31

rect because, they stated, metaplasia is always found in connection with regenerative processes.

Logie [18] reported the presence of "pale epithelium" in 60 per cent of 330 malignant and nonmalignant tumors of the breast. Foote and Stewart found some form of hidradenocytic epithelium in 42 per cent of breasts that were free of cancer and in 39 per cent of breasts that were the site of cancer; the incidence according to age, as reported by them, is given in table 2.

We examined a series of 300 female breasts removed because of a nodular carcinoma and not showing any gross evidence of cystic disease. Our findings are summarized in table 3. The increase in frequency of

16. Borchardt, Moritz, and Jaffé, Rudolf: Zur Kenntnis der Zystenmamma, Beitr. z. klin. Chir. **155**:481-514, 1932. Korpassy, Bela: Systematische Untersuchungen über Epithelveränderungen in der weiblichen Brustdrüse in ihren Beziehungen zum Alter des Individuums und zum Krebs der Mamma, Virchows Arch. f. path. Anat. **299**:793-810 (June) 1937.

17. Berning, H., and Bücker, J.: Quoted by Logie, J. W.: Mastopathia Cystica and Mammary Carcinoma, Cancer Research **2**:394-397 (June) 1942.

18. Logie, J. W.: Mastopathia Cystica and Mammary Carcinoma, Cancer Research **2**:394-397 (June) 1942.

occurrence of hidradenocytic cysts with age would indicate that they were not formed in utero but were the result of proliferative processes which occurred in the breast. While all these breasts contained a nodular carcinoma, the sites of the cysts bore no relation to the position of the carcinoma in the breast but were scattered throughout the organ.

CONCLUSIONS

1. The hidradenocyte is a specific cell type which secretes in apocrine fashion and has for its specific cellular products eosinophilic, siderophilic, fuchsinophilic and sudanophilic inclusions, as well as large amounts of cholesterol.

2. The hidradenocyte may be most accurately identified by a polychromatic staining method devised by Lendrum and modified by us.

TABLE 3.—*Incidence of Hidradenocytic Cysts in 300 Female Breasts Removed Because of Nodular Carcinoma and Not Showing Gross Evidence of Cystic Disease*

		Cases of Hidradenocytic Cysts	
Age, Yr.	Total Cases	No.	%
13-39	50	10	20
40-59	150	70	47
60 or more	100	62	62

3. The hidradenocyte secretes in apocrine fashion as, at least in part, does the mammary alveolar epithelium. It is, however, a distinct cell type and is not to be regarded as a degenerated form or "residual lactation acini" derived from the latter epithelium by physiologic changes of menstruation or lactation.

4. The presence of iron granules as a means of identifying the hidradenocyte has been unduly stressed. Iron granules do occur, but they are so infrequent as to offer no practical aid in identifying this cell.

5. Small hidradenocytic cysts are a constant feature of the cystic breast.

6. The mammary alveolar epithelium and the hidradenocytic epithelium form cystic structures by the process of secretion. This secretion in large part is responsible in the case of the papilloma for the discharge from the nipple. This discharge is in many cases not hemorrhagic, and it is not due solely to infarction of the papilloma, although this is a rather frequent finding.

7. The blue-domed cyst is lined by hidradenocytes and contains cholesterol which is a specific secretory product of this cell.

8. The extramammary hidradenoma (of the vulva, anus and so forth) and the intracanalicular papilloma of the breast are one and the same tumor.

9. The characteristic cells of the hidradenoma and papilloma are the usual type of glandular epithelium, the hidradenocyte, the myoepithelium, "clear cells" resembling those of the pars secretoria of the eccrine sweat glands and sebaceous-like cells. In addition, mucus-secreting cells have been identified in both tumors.

10. The presence of these unusual cell types in a papilloma or hidradenoma does not indicate malignant change.

11. The incidence of small hidradenocytic cysts in breasts that are the site of nodular carcinoma increases progressively with age. Their increase with age and their presence in papillomas speak for their origin in proliferative and metaplastic processes. They are clearly not degenerative forms.

12. Comedo mastitis of the ordinary type is an anomaly of secretion; it involves the ordinary ductal epithelium. Comedo mastitis of the hidradenocytic type is a distinct pathologic entity. Either the large ducts beneath the nipple are replaced in their lining epithelium by hidradenocytes or the hidradenocytic alveoli have greatly hypertrophied and replaced the normal structure. Clinically, comedo mastitis of the hidradenocytic type is usually diagnosed as intracanalicular papilloma because of the discharge from the nipple. Both lesions contain hidradenocytes which are responsible for the peculiar secretion.

13. The intraductal carcinoma and Paget's disease bear no relation to the hidradenocyte.

14. No evidence can be found to support the idea of a "sweat gland carcinoma" of the breast. The hidradenocyte has never been observed as an integral part of a malignant lesion.

TREATMENT OF FAR ADVANCED CARCINOMA OF THE BREAST

Present Status of Testosterone Therapy

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THIS report is concerned with the experiences of my colleagues and me during the past three years in the use of testosterone in the treatment of 18 patients with far advanced carcinoma of the breast. From these experiences we have drawn certain conclusions as to its place in the treatment of this type of malignant growth.

Although carcinoma of the breast averages about 20 to 25 per cent of all cancer in women and in them is the commonest form of the disease,[1] it is less rapidly fatal than most neoplasms of this histologic type.

The life expectancy of untreated patients has been repeatedly computed and averages about three and a third years. For this reason the custom of speaking of two, three or five year survivals in measuring the efficacy of any given form of treatment for cancer of the breast is of doubtful value. Cade [1a] has pointed out that the normal life expectancy of a 55 year old woman is about nineteen years (18.77 years) and that for those in whom cancer of the breast develops at that age this average is reduced by from six to fifteen years depending on the grade of malignancy, the extent of its spread at the time of discovery and the type of treatment employed. Since a large percentage of this group of patients ultimately exhibit far advanced lesions no longer amenable to surgical treatment or roentgen therapy, it is to be expected that most of them will gravitate to large medical centers. Thus, in the Surgery Clinic at the University of Michigan the incidence of far advanced carcinoma of the breast is much higher than that in the average surgical practice.

From the Department of Surgery, University of Michigan Medical School.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

Dr. Isadore Lampe, Professor of Roentgenology, University of Michigan, assisted in the roentgenologic aspects of this work.

The testosterone used in this study was supplied through the courtesy of the Schering Corporation and of Dr. Edward Henderson, Bloomfield, N. J.

1. (*a*) Cade, S.: Carcinoma of the Breast, J. A. M. A. **38**:1083-1087 (Dec. 11) 1948. (*b*) Jones, H. W., Jr.: Carcinoma of the Breast, Am. J. Surg. **77**:696-704 (June) 1949. (*c*) Michigan Cancer Bulletin, vol. 2, no. 1, 1948.

From the early reports [2] on the use of testosterone in the treatment of this far advanced lesion, no longer amenable to surgical treatment or irradiation, it appeared that the average life expectancy might be slightly increased as a result of its administration.

The radical operation for cancer of the breast offers the best chance of cure. Other treatments, such as preoperative and postoperative irradiation, therapeutic castration and hormone therapy, are admittedly only adjuncts to surgical intervention. The use of hormones in the treatment of cancer of the breast has more justification, however, than mere simplicity of administration. The incidence curve of breast cancer in females is highest at the age of 45, while the average age at menopause is about 46 years. A secondary peak incidence of breast cancer is at about the age of 60, when ovarian activity finally comes to a complete standstill.[3] These figures suggest some relation between the onset of a change in hormone balance and the development of carcinoma of the breast.

The history of the experimentation with male hormones dates back one hundred years. It was in 1849 that Berthold first castrated a rooster and, by implanting the testicles elsewhere, successfully maintained the normal male characteristics of the fowl. Ordinarily such an experiment would have led to further successes along the line of extracting the active principle from testicles. This was precluded by the fact that male hormone is present in exceedingly minute quantities at any one moment in these organs. True male hormone was first isolated from testicles by Lacquer in 1935, but the yield was so small that commercial use was impossible until testosterone was synthesized by Ruzicka and Butenandt in 1936. After the work of Lacassagne [4] on the hormonal pathogenesis of adenocarcinoma of the breast by estrogen, others considered the possibility of counteracting this effect with androgen. Although Ulrich [5] and Loeser [6] reported the effects of testosterone in cancer of the breast as early as 1939, it was not until Huggins [7] demonstrated the effective

2. Adair, F. E., and Herrmann, J. B.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast, Ann. Surg. **123**:1023-1035 (June) 1946.

3. Adair, F. E.: The Use of Male Sex Hormone in Women with Breast Cancer, Surg., Gynec. & Obst. **84**:719-722 (April 15) 1947.

4. Lacassagne, A.: Hormonal Pathogenesis of Adenocarcinoma of the Breast, Am. J. Cancer **27**:217-228 (June) 1936.

5. Ulrich, P.: Testosterone (hormone mâle) et son rôle possible dans le traitement de certains cancer du sein, Acta, Union Internat. Contre Cancrum. **4**:377, 1939.

6. Loeser, A. A.: Male Hormone in the Treatment of Cancer of the Breast, Acta., Union Internat. Contre Cancrum. **4**:375, 1939.

7. Huggins, C., and Hodges, C. V.: The Effect of Castration of Estrogen and of Androgen Injection on Serum Phosphatase in Metastatic Carcinoma of the Prostate, Cancer Research **1**:293-297 (April) 1941.

use of estrogens in prostatic carcinoma in 1941 that interest in hormone antagonism to cancer was aroused in this country.

The optimal dosage of testosterone was unsettled until recently and varied with the method of administration as well as with the purpose for which it was used. In 1942 Farrow and Woodard [8] reported using doses of testosterone administered intramuscularly as small as 5 mg. per day in the treatment of bone metastasis from carcinoma of the breast. Prudente [9] in 1945 advocated intramuscular doses up to 175 mg. per week depending on the grade of cancer concerned. Methyl testosterone when absorbed through the intestinal tract must be given in a dose approximately five times the intramuscular dose of the drug to produce the same effect, and yet Boger [10] in 1945 reported effective treatment of carcinoma of the breast from oral administration of testosterone in doses of only 100 to 200 mg. per week. As recently as 1948 statements were conflicting even as to whether a repeat course of therapy was worth while.[11]

SELECTION OF PATIENTS AND DOSAGE OF TESTOSTERONE

To assemble a group of patients in whom the action of testosterone might be carefully evaluated, it was decided to select patients with certain signs or symptoms that stamped them as invalids of comparatively short life expectancy. The first of these symptoms was pain, which could be measured by the analgesics required for its relief. The second was disability, which could be evaluated roughly according to whether a patient could take care of her own needs (enjoying full activity or at least of "self service" status) or whether she was an invalid (with or without bathroom or chair sitting privileges) requiring some degree of nursing care. This would enable us to select patients who were literally in, or about to enter, a terminal state because of extensive metastasis, perhaps of several varieties.

To delineate our patients further, we accepted only those who were surgically hopeless and certified by the roentgen therapist as unable to tolerate more irradiation. Even the benefits of total body irradiation were exhausted.

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8. Farrow, J. H., and Woodard, H. Q.: The Influence of Androgenic and Estrogenic Substances on the Serum Calcium, J. A. M. A. **118**:339 (Jan.) 1942.

9. Prudente, A.: Postoperative Prophylaxis of Recurrent Mammary Cancer with Testosterone Propionate, Surg., Gynec. & Obst. **80**:575-592 (June) 1945.

10. Boger, W. P.: Methyl Testosterone in Surgical Castration in Treatment of Carcinoma of the Breast, J. Clin. Endocrinol. **6**:88-98 (Jan.) 1946.

11. (*a*) Cutler, M., and Schlemenson, M.: Treatment of Advanced Mammary Cancer with Testosterone, J. A. M. A. **138**:187-190 (Sept. 18) 1948. (*b*) Herrmann, J. B.; Adair, F. E., and Woodard, H. Q.: The Use of Testosterone Propionate in the Treatment of Advanced Carcinoma of the Breast: II. The Treatment of Osseous Metastases, Surgery **22**:101-119 (July) 1947.

Although it had been pointed out by Geist, Salmon and Hambleu [12] in 1941 that testosterone was equally effective by any method of administration, it quickly became apparent, in treating patients with carcinoma of the breast, that the effectiveness of the oral dose was poorly controlled in some patients because of coincidental nausea and vomiting. Further variation was accounted for by a tendency on the part of other patients to hold the tablet in the mouth for some time, permitting absorption directly through the oral mucous membrane, where it is over three times more potent than when absorbed through the intestinal mucosa.

Although we have used subcutaneously implanted pellets occasionally as a supplementary form of treatment, we found that patients given these were less reliable in reporting for frequent check-up examinations than those who must report regularly, every other day or every week, for their intramuscular injections. For these three reasons it has seemed that intramuscular administration of testosterone propionate in oil was the most satisfactory method for both the physician and the patient.

Even as the amount and method of testosterone administration is largely unsettled, so is the optimum frequency of administration undecided. In the present study, it was decided that the starting dose would be 250 mg. of testosterone propionate in oil administered intramuscularly every other day for a total of 2,500 mg. as an intensive course of therapy. This was to be followed by a waiting period that would depend entirely on the response of each patient. It is clear from figure 2 that the plan was kept flexible enough to suit the needs of the individual patient. Patient G. S. (fig. 2), for example, was treated from the beginning with interrupted intensive courses of therapy. Patient D. H., on the other hand, began with the interrupted intensive course plan. After the third course, she complained of the cyclic effects of the treatment, particularly the restlessness that consistently appeared at the middle of her intensive courses, and of depression and weakness when the drug was wearing off. She was changed to a weekly dose routine, receiving 250 mg. every week, and was continued on this regimen for most of her remaining life. Increasing the dosage to 375 mg. per week during the last six weeks of life failed to modify a later acceleration of her downhill course.

In addition to these variations in dose routine, the appearance of excessive pain or vomiting occasionally caused the total dosage per course to be reduced to one half, or 1,250 mg. When the early response to the intensive course seemed less than expected, the 2,500 mg. was occasionally increased to 3,750 mg. or perhaps was supplemented by the subcutaneous implantation of pellets. These variations in treatment appear in figure 2.

12. Geist, S. H.; Salmon, U. J., and Hambleu, E. C.: Androgen Therapy in the Human Female, J. Clin. Endocrinol. **1**:154-186 (Feb.) 1941.

The life span in years of our patients after the discovery of the tumor is compared in figure 1. The period of testosterone therapy of each patient in figure 1 is magnified in figure 2, where the number of days of survival of each patient after the use of testosterone was started has been expanded in the form of a graphic protocol. Since none of our patients was accepted for treatment until pain requiring narcotics or disability requiring nursing care had developed, it is apparent that both the weekly maintenance doses and the interrupted intensive course

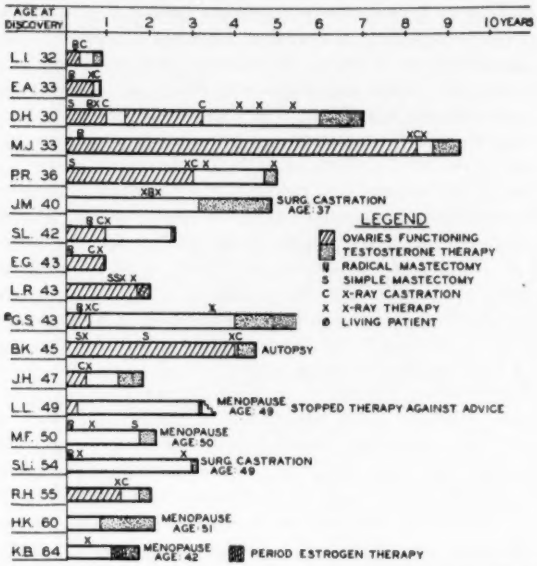


Fig. 1.—Life span in years after discovery of tumor. The length of time each patient received testosterone is graphically compared with the total period during which each patient was known to have breast cancer. No patients received testosterone until they had sufficient pain to require narcotics and/or were so incapacitated by their malignant disease as to require nursing care. Clinically a life expectancy of over one to four months would not have been entertained in any case. When this is kept in mind, a survival of a year or more on testosterone becomes significant even though the patient may have lived five years or more with the tumor before testosterone was given; for patients J. M., G. S. and H. K. the survival period on testosterone therapy was from 30 to 60 per cent of their total survival period after the development of tumor.

may offer relief for over a year but that the drug eventually fails to produce symptomatic improvement.

After a varying interval entirely free of treatment following the first intensive course, the patient was carried on either a single weekly dose

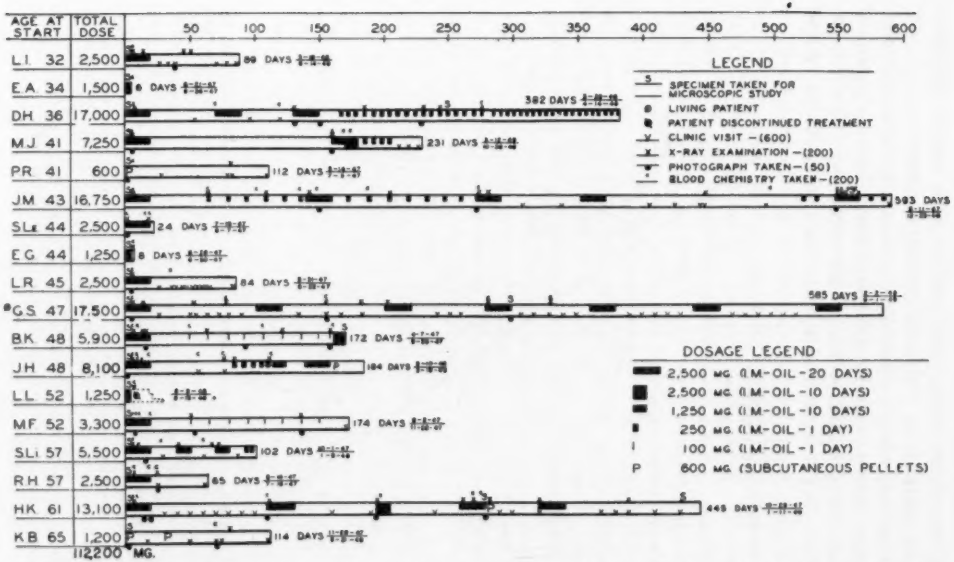


Fig. 2.—Life span in days. This chart is a clinical protocol in graphic form of the survival periods of 18 patients on testosterone. Since all patients met approximately the same requirements for treatment and since no common denominator was found to distinguish those who enjoyed improvement from those who did not, the variability in the survival times of D. H., J. M., G. S. (who has lived over two years at the time of this writing, Feb. 16, 1950) and H. K. as compared with others less fortunate emphasizes the unpredictability of success in treatment with testosterone other than by a clinical trial of the drug.

routine or an intensive course of 2,500 mg. in twenty days at intervals dictated by the reappearance of pain or disability. We found that in the last analysis such "demand therapy" has led to an over-all average of 200 to 300 mg. of testosterone per week for each patient. Figure 3 illustrates the source from which this statement is drawn.

To both patients and physicians the cyclic improvements seen with the interrupted courses may be more impressive than the plateau of response maintained by the weekly or biweekly dose. However, the average patient may find more composure with a dose sufficient to keep

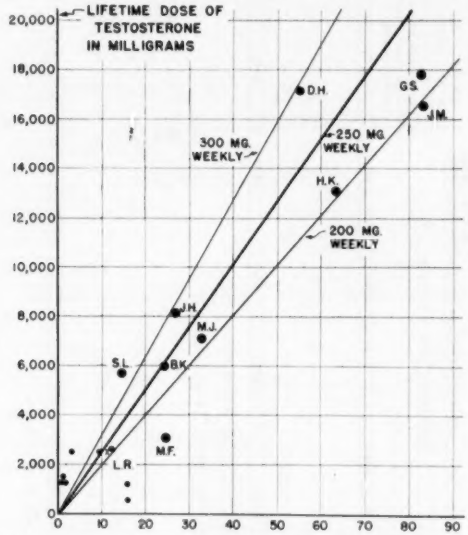


Fig. 3.—Life span in weeks on testosterone therapy (average dose 250 mg., for maximum benefits and minimal side effects). The significant points plotting dosage in milligrams against survival time in weeks are located on this chart as black dots labeled with the patients' initials. Since therapy was repeated only on patient's demand when relapse occurred, it is not surprising that no average doses were exactly the same. Superimposed on this scatter chart are a number of straight lines that plot an arbitrary average dose of 300, 250 and 200 mg. weekly. It is apparent that all patients who lived for a significant period (over one hundred days) fall close to or between the lines represented by a dosage of 200 to 300 mg. per week (equal to 30 to 45 mg. per day). Among 7 patients on "demand therapy" who lived over six months (twenty-four weeks), it is seen that a therapeutic dose of testosterone has uniformly approached an average of 250 mg. weekly.

her symptom free than when awaiting a relapse as a sign that reinstitution of intensive therapy is indicated.

In 2 patients the drug was administered directly into tumor tissue (in metastatic supraclavicular nodes and in the primary tumor of patient

H. K. and into the recurrent lesion of patient D. H.). In these patients it appeared no more effective than when given intramuscularly.

The use of testosterone in conjunction with surgical intervention, roentgen therapy, sodium pteroyl triglutamate (teropterin®) or castration, has been reported by several authors.[13] By avoiding the coincidental combination of these measures we have attempted to provide a more accurate evaluation of the results that may be obtained with testosterone alone. Whether some combined form of therapy may eventually prove to be more desirable must await further study.

The subject of surgical and roentgen ray castration in the treatment of patients with cancer of the breast has been open to wide discussion. Work by Geist and others [14] has shown that testosterone can suppress menses in premenopausal women in doses of 500 mg. or more per month. One patient has been reported as entirely asymptomatic from painful bone metastasis as long as she was kept amenorrheic by means of the androgen.[11b] In spite of these findings it is admitted that as long as the ovaries are not totally defunctionalized by roentgen or surgical castration, ovarian activity is difficult to evaluate in any particular patient. The menopause itself does not necessarily mean a complete cessation of ovarian activity, but it at least indicates a marked decrease, with relatively little monthly fluctuation.

It has been pointed out by Herrmann, Adair and Woodard [15] and confirmed by others that high estrogen levels in the premenopausal patient with carcinoma of the breast commonly results in a rapid downhill course. Such a level may result from the administration of estrogens for menopausal syndrome or from pregnancy. The rise in libido that sometimes accompanies androgen administration plus the false security that may be aroused by the concurrent amenorrhea commonly incurred in the premenopausal group may result in an increased hazard of pregnancy since large doses of testosterone do not uniformly preclude conception. For this reason castration by means of either roentgen rays or surgical procedure is indicated before testosterone therapy is begun.

All but 1 of the patients in this series had been castrated at least three months prior to the institution of androgen treatment. All but 2 patients preferred roentgen ray to surgical castration. One patient with a large sarcoma of the breast refused castration and yet was accepted, as a control patient, for testosterone administration.

13. Carlile, T.: Regression of Pulmonary Metastases from Carcinoma of the Breast, Bull. Mason Clin. **2**:118-121 (Dec.) 1948. Boger.[10] Prudente.[9]

14. Geist, S. H.; Salmon, V. J.; Gaines, J. A., and Walter, R. S.: The Biologic Effects of Androgen (Testosterone Propionate in Women), J. A. M. A. **114**:1539 (April 20) 1940.

15. Herrmann, J. B.; Adair, F. E., and Woodard, H. Q.: Effect of Estrogen Hormone on Advanced Carcinoma of Female Breast, Arch. Surg. **54**:1-9 (Jan.) 1947.

Thus, the following criteria were the basis for selection of patients in this study: (1) a diagnosis of far advanced cancer of the breast with a variety of metastasis; (2) all the surgical treatment practicable completed; (3) benefits possible from roentgen therapy exhausted; (4) establishment of a postmenopausal status, either natural or from irradiation or surgical castration brought about at least three months before start of use of testosterone, and (5) development of pain of cancer origin requiring narcotics for relief and/or disability requiring nursing care. No attempt was made to select patients or to vary the androgen dosage or administration according to histologic classification of the tumor or its degree of undifferentiation.

SIDE EFFECTS OF TREATMENT

In all patients receiving androgen therapy one or more of the undesirable side effects such as hirsutism, lowering of pitch and huskiness of the voice, hypertrophy and increased irritability of the clitoris, dysuria and vaginal discharge were noted in some degree. Nervousness is occasionally experienced but is readily amenable to mild sedation. Nausea or vomiting, if a predominant feature in the patient's illness, may be increased with the administration of testosterone. Stiffness and lameness and even pain may be temporarily increased. Other side actions may be temporary swelling of soft tissues either locally in the face, arms, legs or eyelids or even of a more generalized type like a mild anasarca.

An increased blood calcium level has been offered as a contraindication to the administration of testosterone in patients with bone metastasis.[16] Cutler and Schlemenson [11a] have stated more recently that increased calcium is not a contraindication to the use of this hormone. Seven of our patients had an increase in blood calcium at the time they were accepted for therapy. All these had bone metastasis. No consistant rise or fall in the calcium level under the influence of testosterone was noted in our patients. It is felt that increase of blood calcium over 17 or 18 mg. per hundred cubic centimeters or the appearance of clinical symptoms of hypercalcemia should be an indication to stop the use of the drug temporarily. Certainly a patient who has a renal calculus, for example, should be followed carefully for progression of that lesion.

None of the patients in this series had evidence of thyroid disease at the onset of treatment, and yet patient G. S., after her third intensive course of treatment on about her two hundredth day of survival from the beginning of testosterone treatment, complained of pressure in her

16. Farrow, J. H.: The Effect of Sex Hormones on Skeletal Metastases from Breast Cancer, Surgery **16**:141-151 (July) 1944. Adair and Herrmann.[2] Farrow and Woodard.[8] Herrmann and others.[11b]

neck and of subjective interference with breathing. Examination disclosed a diffuse but asymmetric enlargement of the thyroid. The enlargement disappeared within two months and has never returned. The development of goiter has been noted in other forms of testosterone therapy.[17]

The most serious complication that appeared in some patients while under treatment was shortness of breath. This is usually due to the accumulation of pleural fluid and is most alarming when effusion is already present from intrathoracic metastasis. The effusion is usually of short duration and yet may develop rapidly in amounts large enough to require thoracentesis on one or more occasions until regression occurs. In only 1 patient were carcinoma cells demonstrable in the pleural fluid.

*Results of Treatment Plotted Against Survival**

Survival	Number of Patients†	Good Response			Slight Improvement			No Improvement		
		No. of Patients	Name	Age‡	No. of Patients	Name	Age‡	No. of Patients	Name	Age‡
Up to 1 yr	2	1	H. K.	60	0	.....	..	1	L. I.	32
1 to 2 yr	4	2	J. H.	47	1	R. H.	55	1	K. B.	64
	..	..	M. F.	50	..	.....	..	..	.....	..
2 to 3 yr	1	0	.....	..	1	S. Li.	54	0	.....	..
3 to 4 yr	2	2	J. M.	40	0	.....	..	0	.....	..
	..	..	G. S.	43	..	.....	..	..	.....	..
4 to 5 yr	2	1	B. K.	45	1	P. R.	36	0	.....	..
5 to 6 yr	0	0	.....	..	0	.....	..	0	.....	..
6 to 7 yr	1	1	D. H.	30	0	.....	..	0	.....	..
7 to 8 yr	0	0	.....	..	0	.....	..	0	.....	..
8 to 9 yr	1	0	.....	..	1	M. J.	33	0	.....	..
Total	13	7	.....	..	4	.....	..	2	.....	..

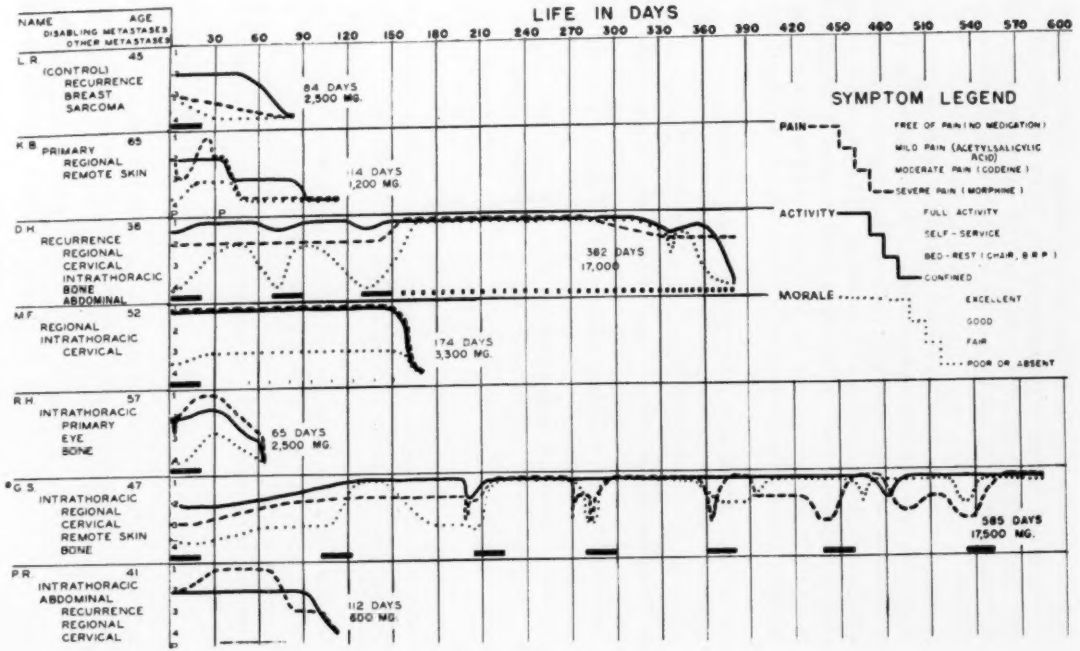
* Number of years patient was known to have had cancer before start of testosterone.
† List includes only those patients who survived over thirty days after start of testosterone.
‡ Age at time cancer was discovered.

Accurate evaluation of the physical signs of pleural fluid is difficult in chests made asymmetric from previous operation or irradiation. A baseline roentgenogram of the chest is, therefore, important prior to the institution of treatment with testosterone for far advanced carcinoma of the breast.

The results of our experience with testosterone therapy are described in terms of symptoms and signs. A summary of response to treatment in terms of pain, freedom of activity and sense of well-being is seen in figure 4, in which graphic profiles are used for comparing these symptoms in all patients who lived over thirty days.

The response to this form of therapy has been wholly unpredictable, and therefore comparison between response, duration of disease, age of

17. Moehling, R. C., and Gerisch, R. A.: Methyl Testosterone for Migraine of Women. J. Michigan S. M. Soc. **48**:1025-1028 (Aug.) 1949.


NAME AGE
DISABLING METASTASES
OTHER METASTASES
LIFE IN DAYS
30 60 90 120 150 180 210 240 270 300 330 360 390 420 450 480 510 540 570 600
L.R. 45
(CONTROL)
RECURRENCE
BREAST
SARCOMA
84 DAYS
2,500 MG.
K.B. 65
PRIMARY
REGIONAL
REMOTE SKIN
114 DAYS
1,200 MG.
D.H. 38
RECURRENCE
REGIONAL
CERVICAL
INTRATHORACIC
BONE
ABDOMINAL
382 DAYS
17,000
M.F. 52
REGIONAL
INTRATHORACIC
CERVICAL
174 DAYS
3,300 MG.
R.H. 57
INTRATHORACIC
PRIMARY
EYE
BONE
65 DAYS
2,500 MG.
*G.S. 47
INTRATHORACIC
REGIONAL
CERVICAL
REMOTE SKIN
BONE
585 DAYS
17,500 MG.
P.R. 41
INTRATHORACIC
ABDOMINAL
RECURRENCE
REGIONAL
CERVICAL
112 DAYS
600 MG.
SYMPTOM LEGEND
PAIN
FREE OF PAIN (NO MEDICATION)
MILD PAIN (ACETYLSALICYLIC ACID)
MODERATE PAIN (CODEINE)
SEVERE PAIN (MORPHINE)
ACTIVITY
FULL ACTIVITY
SELF-SERVICE
BED-REST (CHAIR, B.R.P.)
CONFINED
MORALE
EXCELLENT
GOOD
FAIR
POOR OR ABSENT

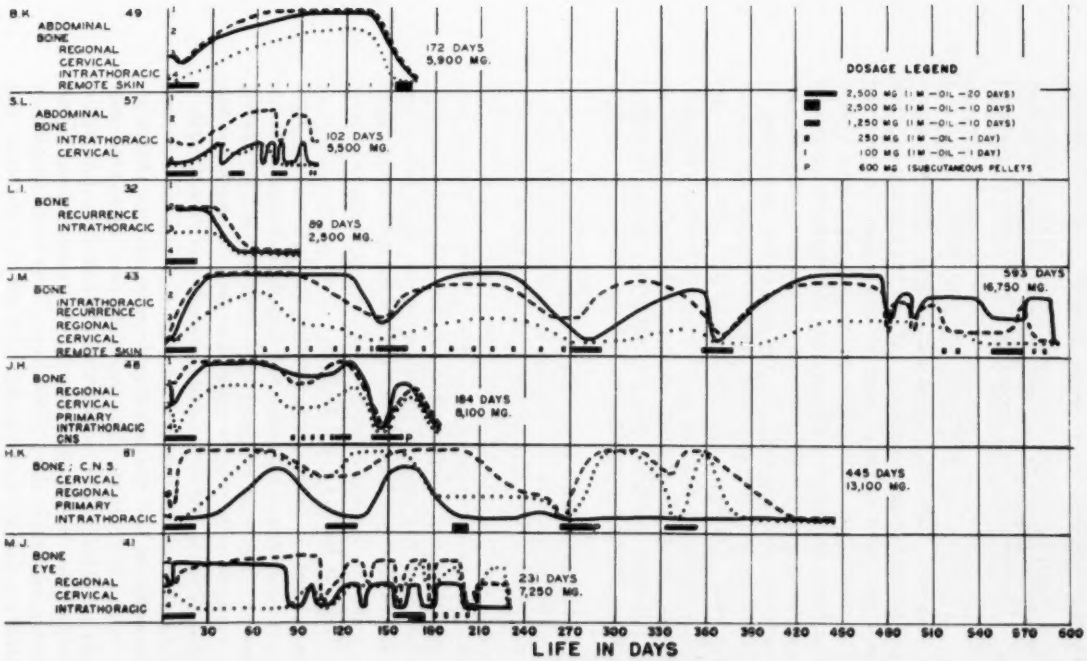


Fig. 4.—Comparative graphs of pain, activity and morale in testosterone-treated patients grouped according to their disabling metastasis. Downward curves illustrate worsening of symptoms. Rising curves indicate improvement. The effectiveness of testostrone in bringing about improvement on repeated occasions in the same patient after numerous relapses is best illustrated in the graph of J. M., a patient disabled by painful bone metastasis but bearing other extensive metastatic lesions as listed in the column to the left. Although this chart shows only her favorable response in respect to three symptoms, her improvement was generalized during all five cycles that appear in her five hundred and ninety-three day survival. D. H. demonstrates the plateau of improvement that may appear if weekly maintenance doses of 250 to 300 mg. are substituted for the 2,500 mg. treatments at intervals on demand.

patient and location of metastasis has been unprofitable in the estimation of benefit or prolongation of life under treatment (see accompanying table).

The response of patients to treatment, while not consistent, was often dramatic. This response is well demonstrated by the following selected summaries.

SUMMARY OF RESPONSES TO TREATMENT

Pain, Lameness, Stiffness, Strength and Activity.—J. M. was admitted as a bed patient because of weakness, stiffness and lameness and such severe back pain from extensive bone metastasis that she had been receiving frequent doses of morphine sulfate for one week. Within twenty-four hours after her first 250 mg. dose of testosterone propionate adequate analgesia was obtained with codeine, and after three days no further narcotics were required. By the end of her first course of therapy (2,500 mg. in twenty days) she was free from pain and walking around the ward. On return home she took up light duties and found that within a month she was able to drive a farm tractor and to help with plowing. Symptoms returned in three months, but response to treatment was again rapid, and this response was repeated on several more occasions during her survival for five hundred and ninety-three days (fig. 4).

The usual initial response of patients is temporary increase of pain, stiffness and lameness that on occasion may increase the narcotic requirements. For example, this same patient, J. M., returned to the clinic in moderate pain requiring codeine on her three hundred and sixtieth day of survival. At the beginning of an intensive course of therapy, pain was so intensified that morphine was required for about six days. Toward the end of this course of treatment the pain again became less marked, and twenty days after she left the hospital only acetylsalicylic acid was required. A similar response was seen in several additional patients (G. S., B. K., S. Li. and H. K.).

Patients' Morale.—Authors have reported that patients have noted a rise in morale or sense of well-being following the institution of testosterone therapy. This response has been a prominent and outstanding aspect of treatment in the patients reported on here. It closely parallels the response curves of decrease in pain and improvement in strength.

Weight and Appetite.—Most patients observed a remarkable increase in appetite within the first few days after the commencement of therapy, and body weight usually showed a corresponding rise. Rapid initial gain was usually accounted for by the temporary gross swelling of metastatic lesions and early but fleeting appearance of subcutaneous edema. These effects usually subsided in three to ten days. The average weight gain of the patients in this series twenty days after the start of therapy was

5 pounds (2.3 Kg.), and their average gain at three months was 4 pounds (1.8 Kg.). All patients eventually lost weight before death.

Libido.—Of particular interest is the remarkable rise in libido shown by a few persons. M. J., aged 41, who showed in some ways only a mediocre to a fair response to testosterone in comparison with other patients, nevertheless had a remarkable rise in libido beginning with her second intensive course of testosterone therapy in the hospital (one hundred and sixty-fifth day of treatment).

Another patient, G. S., aged 47, had noted marked waning of sex interest since castration six months previously. There was a moderate rise in libido during her first course of testosterone therapy, and this became pronounced with the second course. To the present she has reported a cyclic one month rise, one month crest and one month decline in libido after seven successive courses of therapy.

A similar but less pronounced effect was noted by patient D. H. In this patient when the intermittent intensive course of therapy was changed to the 250 mg. weekly dose the cyclic effect disappeared and a fairly high libido was maintained for about three months, gradually declining to zero about a month before her death. Decline of libido in a patient formerly stimulated in this respect is one of the earliest signs of waning androgen effect.

Masculinizing Effects.—Brunettes were more prone than blondes to increased hair on the extremities, the upper lip and the chin. Peaking of the pubic hair line or temporal recession of hair was not noted in the patients reported on here.

Mild deepening of the voice has been common but rarely of much concern to the patient. G. S. noted that a rise in her voice pitch was invariably followed shortly by other symptoms demanding further treatment.

Many patients showed a detectable increase in the size of the clitoris. In 2 patients this organ doubled its size in six months. In a third patient it enlarged to three times its normal size in the first four months after the beginning of androgen administration. However, it remained unchanged during the following year and a half while the patient was receiving similar additional treatment.

No patients in this series suffered from acne while receiving treatment.

Atrophy of breast tissue was not observed in patients who maintained favorable balance in weight.

The degree of masculinization as a result of the administration of androgen to the 18 patients in this series was not closely related to the size of the dose. The most notable evidence of masculinization occurred in K. B., aged 65, after the implantation of 1,200 mg. of testosterone pellets. Formerly she had failed to respond well to estrogen therapy.

Most observers have noted some change in the tissue in breasts with cancer after the initiation of testosterone therapy. In the group of patients under observation changes were noted both in soft tissue and in areas of bone metastasis; these changes were highly variable in the same patient and totally unpredictable from one patient to another.

Some of the more striking responses to androgen administration are recorded here.

Recurrence at Site of Primary Tumor.—Injection of 50 mg. of testosterone directly into the base of a large recurrence in the chest wall in patient D. H. resulted in slight decrease in the size of this lesion over a three week period while distant cutaneous metastasis continued to

Fig. 5 (B. K., age 48).—*A*, on the sixteenth day of treatment after 2,000 mg. of testosterone, this patient was well enough to be photographed. Although her metastatic lesions were rapidly receding, some are still visible as nodular swellings in the cervical and supraclavicular regions and a pigmented placque is conspicuous in the skin to the right of the umbilicus. Moderate ascites is present. She complained of painful stiffness of neck and jaw. *B*, on her ninety-fifth day of treatment, after a total of 2,900 mg., all lesions are reduced in size, ascites has subsided and former symptoms of pain and stiffness have disappeared.

enlarge. In another patient (J. M.), within two months after commencement of treatment numerous small local recurrences had disappeared except for pigmentation at the former site of the lesions. At a later date, while this patient was still under treatment, recurrent metastatic lesions reappeared at the same sites.

Regional Soft Tissue Metastasis.—Cervical and supraclavicular metastasis was so extensive in patient B. K. (fig. 5*A*) that stiffness and pain prevented the patient from opening her mouth or from rotating

the head more than 5 to 10 degrees from the midline. These metastatic lesions disappeared almost completely (fig. 5 *B*) by the ninety-fifth day of testosterone therapy. Recurrence of the lesions was well advanced by the one hundred and fifty-sixth day of her survival for one hundred and seventy-two days. Multiple bilateral walnut-sized areas of cervical and supraclavicular metastasis in another patient (H. K.) became 30 per cent larger in the first six days of treatment and yet were scarcely palpable two months later.

Remote Cutaneous Lesions.—After about ten months of treatment with testosterone in J. M. numerous tiny areas of cutaneous metastasis developed over the entire body. These fluctuated in size during the remaining ten months of life. At the time the patient G. S. was first seen, numerous areas of metastasis were present on the scalp. After androgen treatment was started, the largest of these almost completely disappeared and regrowth of hair was fairly normal. This lesion later increased in size and was excised for histologic examination. Other scalp lesions meanwhile remained unchanged for a long period and eventually enlarged, and more recently additional nodules have appeared.

Intrathoracic Lesions.—On all patients a baseline roentgenogram of the chest was made since traumatic or neoplastic asymmetry made evaluation of physical signs questionable. Over half of our patients had intrathoracic metastasis, and in 3 of these (R. H., P. R. and G. S.) such lesions were the presenting disability. Two patients showed only fair response to treatment, one living sixty-five days and the other one hundred and twelve days. Although testosterone therapy produced some improvement, especially in the control of pain, changes in the parenchymal spread were not well defined. The third patient, G. S., presented herself to us with pleural and pulmonary metastasis that incapacitated her from weakness, shortness of breath and pain in her back and chest (fig. 6 *A*). Pleural effusion had required thoracenteses on many occasions. After a temporary increase of fluid accumulation for the first two weeks of treatment, the process was arrested. She improved rapidly, and the metastatic lesions in the least involved left lung disappeared roentgenologically (fig. 6 *B*). She has survived for over two years at the time of this writing. Temporary effusion developed so rapidly in patient J. M. in her third and fifth courses of therapy that emergency thoracenteses at her bedside were necessary. Smears of her thoracic fluid sediment showed the presence of cancer cells.

Abdominal Metastasis.—Five patients have had abdominal metastasis as their most disabling lesion. Two of these, E. G. and E. A., were moribund at the time therapy was started and neither survived over ten days. Extensive liver metastasis was present at necropsy. Their down-

hill course appeared to be accelerated by the treatment. P. R. and S. Li. were both seriously ill when treatment was started, and although each survived over one hundred days the effect of testosterone on them seemed of borderline value.

B. K., on the other hand, in spite of extensive abdominal metastasis as well as disabling bone metastasis, responded well to testosterone therapy in that an abdominal mass 7 by 7 cm. originally fixed in the right upper quadrant on palpation, although persisting throughout her initial course of therapy, was found to have disappeared entirely on physical examination two months later. At the time of her final admission, about one hundred and sixty days after the start of her treatment, it was again present and at autopsy was confirmed as a metastatic mass associated with extensive carcinomatosis.

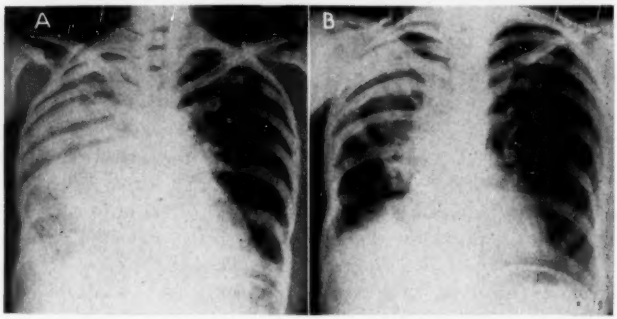


Fig. 6 (G. S., age 47).—*A*, on the twenty-first day of treatment for disabling intrathoracic metastasis, after 2,500 mg. of testosterone propionate, pleural effusion was still developing in this patient and required one more thoracentesis before it began to subside. Note the lymphatic spread from hilar regions on both sides. *B*, by the two hundred and twentieth day of therapy, the patient was symptom free and on the three hundred and fifty-eighth day the above roentgenogram was made. Note the subsidence of pleural fluid on the right and the disappearance of pulmonary involvement on the left.

Metastasis to the Central Nervous System and the Orbital Areas.—One of our patients, M. J., included in this report, had metastasis in both eyes, the left globe being almost completely filled with a metastatic lesion and the right being partially filled. On ophthalmoscopic examination there was no gross regression of these lesions under testosterone therapy. However, it was the opinion of the patient and her husband that the sight in her right eye improved steadily from about the twentieth day of treatment to the time of her death. One other patient not mentioned elsewhere in this survey had metastasis to the brain from far advanced carcinoma of the breast. Paralysis of the sixth nerve which

had developed was considered by her examiners to be due to a growing metastatic lesion. Shortly after testosterone therapy was started the progress of this paralysis was arrested, and eventually full motor activity of the lateral rectus extraocular muscle of the eye was restored.

Bone Metastasis.—The progress of bone metastasis under the influence of testosterone was apparently altered in every instance in our patients. The most striking changes of osteoblastic nature were in

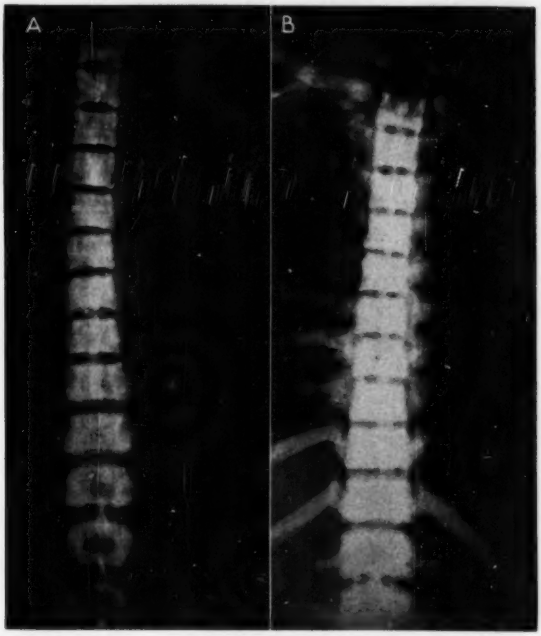


Fig. 7 (B. K., age 49).—*A*, an admission roentgenogram of the spine of this bed patient shows extensive osteolytic invasion of the spine and a generalized osteoporosis. *B*, on the one hundred and fifty-eighth day of treatment, after only 2,500 mg. of testosterone, extensive osteoblastic change has appeared and remineralization is evident. Microscopic examination of autopsy material from this spine showed heavy laminations of bone newly laid down replacing tumor tissue in former marrow spaces.

patients B. K., J. M. and H. K. The vertebral lesions of B. K. (fig. 7) and J. M. in particular became so densely calcified that bone pattern was nearly lost on roentgen examination. Two extensive lytic lesions in the pelvis of M. J. had become repaired by irradiation, but the use of testosterone resulted in a far denser remineralization. While a large

lytic lesion in this patient's left proximal ulna showed osteoblastic repair, there was a simultaneous rapid development of a destructive lytic lesion in the distal shaft of the same bone (fig. 8).

Just before her fourth course of therapy a pathologic fracture developed at the site of a large lytic lesion in the lower shaft of the left femur in patient H. K. Union was complete both clinically and by roentgen examination after four months in a hip spica. A month later she incurred

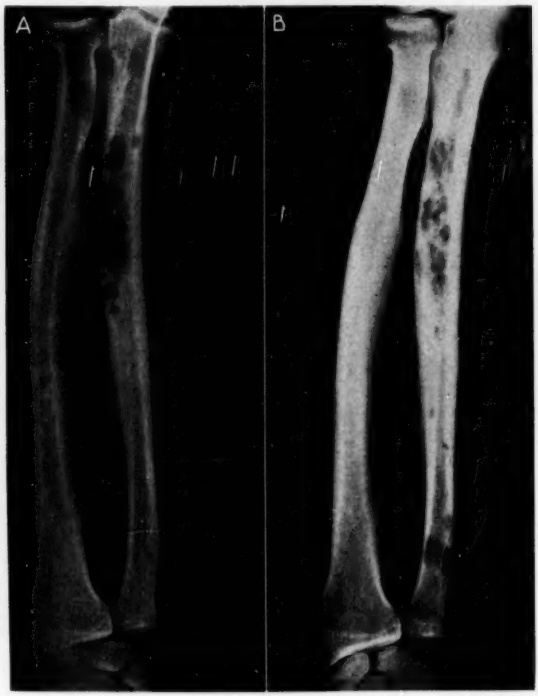


Fig. 8 (M. J., age 41).—*A*, an admission roentgenogram of the right forearm shows an extensive osteolytic lesion in the upper half of the left ulna. *B*, after 2,500 mg. of testosterone, there is marked osteoblastic change in this lesion on the fifty-fifth day, with generalized remineralization. Simultaneously a new osteolytic lesion, barely visible on the admission roentgenogram, has rapidly increased in size in the distal third of the same bone.

two new spontaneous fractures (right radius and left sixth rib). By the time of her death two months later the rather heavy callus at the femur fracture site had been reabsorbed, and there was no evidence of repair at autopsy.

G. S. had a single lytic lesion in the body of the third lumbar vertebra which became calcified in about eight months and has remained unchanged up to her twentieth month of treatment.

Two patients, S. Li. and S. Le. (the latter not mentioned on charts) continued to show rapid osteolytic spread of metastasis in spite of treatment.

The relief of bone pain in patient J. M. was far more rapid (twenty-four hours) than could be accounted for by remineralization of the bone lesion. S. Li. also had relief of pain in spite of her failure to show osteoblastic change. Osteolytic lesions often continued to appear even in patients who noted relief from pain with predominantly osteoblastic change.

SUMMARY

The data accumulated on 18 patients who have been treated with testosterone over the past two and a half years have shown that in a given patient who has passed beyond the scope of surgical attack and in whom further response to roentgen therapy is unlikely androgen therapy may reduce the discomfort associated with generalized metastasis from the primary neoplasm and in some cases prolong the life span to an unpredictable length.

In the observations on the group of patients under scrutiny here, no yardstick has been apparent whereby the effect of androgen therapy could be anticipated. The most assured fact gained from our study of these patients has been a total inability to determine the degree and character of improvement that might be expected once androgen therapy has begun, the course or progress of the metastatic lesion as determined on repeated clinical examination and the prolongation of life which might be anticipated. As a result of these observations, no patient with far advanced cancer of the breast seen in the Surgery Clinic of the University Hospital is refused testosterone therapy (providing all the more commonly accepted means of therapy have been exhausted) until a trial course of treatment, in the manner described previously, has been attempted. If relief of symptoms does not result from this measure and if the patient's course is steadily or rapidly worsened as a sequel to the treatment, then only is the use of testosterone discontinued.

Five of the patients included in this report failed to survive thirty days, and their terminal course appears to have been little affected by the method of treatment under consideration. Thirteen of the patients have lived more than thirty days. Two of the 13 showed little or no improvement from testosterone therapy, while 4 others were minimally improved. At the other extreme are patients whose response has been both dramatic and sustained (see the table). As a result of the improvement manifested in a majority of these patients who survived more than thirty days, the average survival time of the 13 patients has been two

hundred and fifty days. The prolongation of life and the relief of disabling symptoms in that group of patients surviving the longest is most striking when it is recalled that each was entering a state of progressive deterioration and invalidism from pain or disability at the time androgen therapy was begun. In the group of patients living more than thirty days, approximately four fifths (79 per cent) of the survival time was so relatively free of pain that simple analgesics (salicylates), when relief from pain was indicated, were sufficient. Codeine was sufficient to control discomfort for an additional 14 per cent of this group, and morphine was necessary in only 7 per cent, usually in the terminal phase of their disease.

An over-all evaluation of the activities of these 13 patients shows that over 75 per cent of their survival time after the commencement of androgen therapy was spent either in full activity or at a level at which nursing care was unnecessary; for only 10 per cent of the total patient survival time were they confined to bed and in need of continuous nursing care. These statistics are summarized in figure 9.

After the administration of testosterone, a majority of the patients in this study noted a temporary exacerbation of their symptoms. For the first forty-eight hours after the administration of the androgen there is often an increase in pain, with increasing stiffness and lameness, and cough, dyspnea, anorexia and nervousness are usually exaggerated. Visible and palpable metastatic lesions were frequently noted to increase in size and tenderness during this same period. In the most ideal circumstances this exaggeration of symptoms persisted for only forty-eight hours and then waned. In other patients worsening of symptoms persisted for as long as ten days before improvement became apparent. While it is impossible to draw accurate conclusions from the small group of patients herein reported, it was apparent that those recovering most rapidly from the early, temporary aggravation of symptoms were promised a better degree of palliation than those requiring a more protracted period before improvement began. Also, those showing the most dramatic improvement after the first course of intensive therapy almost invariably showed a favorable response to subsequent administration of the androgen, and in general their life expectancy was also greatest.

The commonest benefit from the administration of androgen has been the relief of pain from bony metastasis. Coincidental with this improvement there has been an increase in activity, increased strength and improvement in the patient's sense of well-being. In patients showing a good response to any given course of androgen, appetite improved generally on the third or fourth day and this improvement was maintained until the waning effect of androgen was evident. A slight huskiness of the voice has been frequently noted beginning on the sixth to the twelfth day after the commencement of therapy, and by the tenth to the

fortieth day of treatment a steady increase in libido has occasionally appeared. The waning effects of the drug have been first apparent in a decrease in libido, followed shortly thereafter by diminishing huskiness of the voice, diminished appetite and body strength and, finally, recurrence of pain and disability.

The response of the soft tissue metastasis from carcinoma of the breast has been highly variable. We have observed lesions in one area of the body disappear, leaving only an area of pigmentation, while similar-appearing lesions elsewhere have increased in size. Remineralization of

PATIENTS LISTED IN ORDER OF LONGEVITY **			PAIN								ACTIVITY								MORALE							
			NONE		MILD		MODERATE		SEVERE		ACTIVE		SELF-SERV		B.R.M.		CONFINED		EXCEL		GOOD		FAIR		POOR	
NAME	AGE	DAYS OF SURVIVAL	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%	DAYS	%
L.R.	45	114	0	0	0	0	28	33	56	67	0	0	62	74	10	12	12	14	0	0	0	0	15	18	69	82
CONTROL SARCOMA																										
G.S.	47	585 #	240	41	306	52	39	7	0	0	476	81	107	18	0	0	2	1	352	60	62	11	124	21	47	8
J.M.	43	593	71	12	385	65	107	18	30	5	261	44	148	25	160	27	24	4	FAMILIAL MELANCHOLIA *							
H.K.	61	445	230	52	104	23	61	14	50	11	FRACTURED FEMUR *								124	28	75	17	128	29	118	26
D.H.	36	382	152	40	230	60	0	0	0	0	334	87	39	10	6	2	3	1	163	43	86	22	73	19	60	16
M.J.	41	231	0	0	156	68	54	23	21	9	0	0	75	32	75	32	81	36	0	0	29	13	104	45	98	42
J.H.	48	184	83	45	62	34	30	16	9	5	73	40	74	40	19	10	18	10	0	0	74	40	81	44	29	16
M.F.	52	174	160	92	0	0	0	0	14	8	160	92	0	0	0	0	14	8	0	0	0	0	147	85	27	45
B.K.	49	172	91	53	34	20	38	22	9	5	64	37	64	37	30	18	14	8	0	0	70	41	50	29	52	30
K.B.	[illegible]																									
P.R.	41	112	51	46	26	23	29	26	6	5	0	0	97	87	8	7	7	6	NO RECORD KEPT *							
S.L.	57	102	0	0	58	57	44	43	0	0	0	0	0	0	45	44	57	56	0	0	0	0	48	47	54	53
[illegible]																										
R.H.	57	65	21	33	28	43	15	23	1	1	0	0	45	69	18	28	2	3	0	0	0	0	35	54	30	46
PATIENT DAYS 3,248			1107		1452		442		247		1368		721		423		291		639		396		863		645	
AVERAGE SURVIVAL TIME IN DAYS 250			85		112		34		19		114		60		35		24		58		36		78		59	
% OF SURVIVAL TIME				34		45		14	7			49		26		15		10		25		16		34		25
PERCENTAGE OF SURVIVAL TIME SPENT IN USEFUL LIVING			← 79 % →				CODEINE		MORPHINE		← 75 % →				INVALID STATE				← 75 % →						DEPRESSED	
			← 93 % →																							

PATIENT IS STILL ALIVE
* OMITTED FOR REASONS STATED
** LIST INCLUDES ONLY PATIENTS WHO SURVIVED OVER THIRTY DAYS

GOOD RESULTS
MEDIOCRE RESULTS
POOR RESULTS

Fig. 9.—Per cent of days spent in useful living while receiving testosterone, in terms of pain, activity and morale. Since clinically it did not seem as if any patient accepted for treatment would live over thirty to one hundred and twenty days, the average survival time of two hundred and fifty days (over eight months) indicates that their life expectancy might have at least been doubled. Since patients accepted for treatment were already taking narcotics or in an invalid state, their improvement from this status for over 75 per cent of their two hundred and fifty day survival suggests that each patient averaged over one hundred and eighty-five days (six months) more of useful living than would have been clinically anticipated without testosterone therapy to help them. Four patients, D. H., J. M., G. S. and H. K., were particularly instrumental in raising the general average since they survived a total of over six years, over 75 per cent of which was relatively free of pain and of nursing care.

bone which is the site of metastatic osteolytic lesions has been observed between sixty and ninety days in patients in whom this phenomenon has occurred.

The present study was carried out when possible as a "demand therapy" plan of administration of androgen. This has resulted in the administration intramuscularly of an average dose of 250 mg. of testosterone propionate in oil per week. In the group of patients studied here, further beneficial effect was not enhanced appreciably by increasing the average dosage to over 300 mg. weekly in any single patient. The side effects of the drug become increasingly unpleasant as the latter dosage is surpassed. The method of administering the drug in weekly doses seemed as effective as interrupted concentrated courses of 250 mg. every other day for ten doses, giving a total of 2,500 mg. in twenty days. Although it is easier to evaluate the end results of treatment in patients given interrupted doses, some patients, though encouraged by the improvement of their symptoms, were much disturbed by the cyclic recurrence of their undesirable symptoms. Our experience, in general, was that the duration of action of the drug remained about the same until the patient's terminal few weeks, thus indicating no evidence of tolerance.

The rapid accumulation of pleural fluid, and occasionally peritoneal fluid, was the only grave complication encountered in the administration of androgen to these patients with far advanced cancer of the breast. In occasional instances emergency aspiration of the rapidly accumulated fluid was necessary. In view of this serious complication, a roentgenogram of the chest has been taken routinely before administration and patients have been rehearsed regarding symptoms of rapidly accumulating fluid in either serous cavity so that prompt recognition and relief measures may be undertaken when these symptoms become alarming.

CONCLUSIONS

1. Testosterone has a definite place in the treatment of patients with far advanced carcinoma of the breast.

2. To clarify results and statistics in the literature, there is a need for more standardization in the selection of patients with cancer of the breast for treatment with testosterone.

3. Testosterone is of palliative value, and its effect on the carcinoma and its ability to relieve symptoms and to prolong life are highly variable and wholly unpredictable.

4. Testosterone may be of maximum value in patients with far advanced carcinoma of the breast with a variety of metastasis when (*a*) all the surgical treatment practicable has been completed, (*b*) benefits possible from roentgen therapy have been exhausted, (*c*) establishment of a postmenopausal status, either natural or from irradiation or surgical castration, has been brought about before the start of testosterone and (*d*) there have been development of pain of cancer origin requiring narcotics for relief and/or disability requiring nursing care.

5. Dosage, methods of administration and precautions in the use of the androgen are suggested, and the response of the patient and the neoplasm are discussed.

6. By treatment with testosterone as outlined, 7 of 13 patients with far advanced, painful and/or disabling cancer of the breast, who lived over thirty days after the start of therapy, were temporarily rescued from entering an invalid state or a terminal narcotic status and reinstated in family, home and society as useful citizens for an average of over a year. An additional 4 patients received enough benefit to have justified the use of the androgen.

DISCUSSION

OF PAPERS BY DRS. LEMMER, WATKINS AND MCDONALD AND KING

DR. EVERETT LEE STROHL, Chicago: I should like to show a patient who has been receiving testosterone for a period of three years and eight months. She underwent radical mastectomy at the age of 30. She had metastasis to the femur at the age of 38.

(Slide) She had received postoperative roentgen therapy and had been sterilized by roentgen therapy at the time of operation. This is the metastatic lesion of the femur as it appeared at the age of 38.

(Slides) These show the patient at the end of one, two and three years. She is well today and carries on active life as a court stenographer.

We have not treated her as Dr. King has done. She has received a total of 22 Gm. of testosterone, and we are now giving her 300 mg. weekly. Some soft tissue metastasis has developed recently and I do not know what procedure to take now.

One should take the family into one's confidence when administration of the drug is started. The marked increase in libido, which occurs frequently, may prove embarrassing to the patient, the husband and the physician rendering the treatment.

DR. EDWARD S. JUDD JR., Rochester, Minn.: I should like to comment briefly on Dr. King's topic, which has been of great interest. I think he was wise in clearly defining his position first of all. He stressed the fact that all patients had received all possible benefits from surgical operations and roentgen ray therapy before he conducted his study. If everyone, in writing on this topic, would use the same limitations, I am sure there would be much less confusion.

We were interested for a time in pellet implantation. We have largely discontinued that procedure now, because it is hard to follow the condition of these patients adequately and to judge just what has happened to them. The course of the lesion is so unpredictable, anyway, that it is difficult to evaluate it. Some of the authors have commented on the question of osseous lesions as compared with soft tissue metastatic lesions. We also have been greatly impressed at times by the disappearance of one lesion simultaneously with the development of another one. Such an occurrence is difficult to explain.

We have much less confidence than some workers in regard to the ultimate outcome in some of the soft tissue metastatic lesions. The most important factor, then, as Dr. King already has hinted, seems to be the general change in the patient. The process of the disease is so entirely unpredictable and so unrelenting in the face of any type of treatment that the actual benefit in the long run, of course, cannot be properly evaluated. However, the morale, which he has stressed so clearly today, is so important that it appears that this type of treatment probably is here to stay.

TRANSESOPHAGEAL LIGATION OF BLEEDING ESOPHAGEAL VARICES

A Preliminary Report of Seven Cases

GEORGE CRILE Jr., M.D.
CLEVELAND

THERE is a group of children and young adults who bleed frequently and severely from esophageal varices. These patients have normal livers and the varices are the result of a congenital block of the portal or splenic veins. If the bleeding could be controlled, these patients would return to perfect health and would have a normal life expectancy.

Splenomegaly secondary to venous stasis is a constant finding in these cases, but it is rare that splenectomy permanently controls the tendency to bleed. Unfortunately, the majority of the patients have had their spleens re moved, and after removal of the spleen it is not possible to use the splenic vein to effect a shunt between the portal and systemic veins.

The young patient whose spleen has been removed cannot be helped by anastomosis of the portal vein to the vena cava. The block, in these cases, is either in the splenic vein proximal to the point of entry of the coronary vein (figure, *1*) or in the portal vein itself (figure, *2*). If the block is in the splenic vein and if the spleen has been removed, the splenic vein cannot be used for anastomosis to the renal vein, nor would any useful purpose be served by anastomosing the normal portal vein to the vena cava (figure).

If the portal vein is the site of the block, it usually is so obliterated and transformed by recanalization and the development of collateral circulation around it that it is impossible to use it for anastomosis to the vena cava.

It is with this small group of cases in which it is not possible to shunt the hypertensive portal system into the vena cava that we are concerned.

CONVENTIONAL METHODS OF TREATMENT

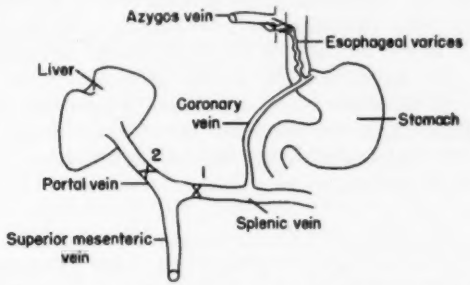
The conventional methods of treatment of bleeding esophageal varices can be divided into (1) operations which attack the problem

From the Cleveland Clinic and the Frank E. Bunts Educational Institute.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

indirectly by attempting to reduce the pressure in the varices and (2) operations which attack the varices directly.

1. *Indirect Attack.*—A. Portacaval Shunts: The various types of anastomosis between the portal and systemic veins are effective in the treatment of portal hypertension secondary to cirrhosis of the liver [1] but are not as often applicable to patients with congenital blocks of the portal vein or its tributaries. End to side anastomosis between the splenic and the renal [2] vein is an excellent method of treating a block in the portal vein, but unfortunately, in our experience the block appeared to be in the splenic vein and the portal vein seemed normal in all but 1 of 7 cases studied. When the block is in the splenic vein, moreover, the vein may be so extensively involved that it is not possible to mobilize enough of it to anastomose to the renal vein. Portacaval anastomosis would be of no value in this situation, and splenectomy alone does not control the bleeding.



Extrahepatic portal obstruction. *1* and *2* are sites of extrahepatic block.

B. Mediastinal Packing [3]: This is designed to lower the pressure in esophageal varices, which is alleged to produce a collateral circulation which helps carry away the hypertensive portal blood. I know of no manometric studies of portal pressure which have been made before and after treatment in these cases to determine whether the operation does diminish portal pressure. It is possible that the benefits that have been ascribed to the procedure are derived from cutting off anastomotic channels from the azygos system rather than from producing them.

1. Blakemore, A. H., and Lord, J. W.: Technic of Using Vitallium Tubes in Establishing Portacaval Shunts for Portal Hypertension, Ann. Surg. **122**:476 (Oct.) 1945.

2. Linton, R. R.: Surgical Treatment of Bleeding Esophageal Varices by Portal Systemic Venous Shunts with a Report of 34 Cases, Ann. Int. Med. **31**: 794 (Nov.) 1949.

3. Som, M. L., and Garlock, J. H.: New Approach to Treatment of Esophageal Varices, J. A. M. A. **135**:628 (Nov. 8) 1947.

Elsewhere in the body scar tissue is thought of as a factor which impedes rather than increases collateral circulation.

One of the patients in this series was treated without benefit by mediastinal packing. Sufficient time has not elapsed in the reported cases to allow appraisal of this method of treatment.

C. Devascularization of the Stomach: On theoretic grounds one would anticipate that complete devascularization of the stomach from esophagus to pylorus would arrest the bleeding in patients who have been subjected to splenectomy. It is difficult to see how the devascularized stomach could transmit hypertensive portal blood to the esophagus in quantities sufficient to cause hypertension and bleeding in esophageal varices. Although ligation of the coronary vein had been abandoned by others because of its failure to alter the course of the hemorrhages, it seemed worth while to attempt to devascularize the stomachs of a group of these patients. All vessels of the stomach down to the pylorus, both arteries and veins (including the gastroepiploic veins through which blood might be transmitted from the pyloric end of the stomach) were removed. The operation is like a total gastrectomy except that the esophagus and duodenum are not transected. Some of the patients did well for periods up to one year after operation, but within two years all of them had had recurrences of their bleeding. However, the bleeding was less severe and less frequent than before the operations in all but 1 case.

D. Total Gastrectomy: This also has been advocated in the treatment of esophageal varices,[4] but it is difficult to see what advantage it would have over devascularization.

E. Splenectomy[5]: Splenectomy alone is rarely effective in controlling the bleeding.

F. Ligation of the Splenic Artery: This may be some value,[6] but I doubt if its benefits would be permanent in severe cases.

2. *Direct Attack.*—A. Resection of the Cardiac End of the Stomach and the Lower Part of the Esophagus[4]: This should be an effective method of dealing with persistent bleeding from esophageal varices.

4. Phemister, D. B., and Humphreys, E. M.: Gastro-Esophageal Resection and Total Gastrectomy in Treatment of Bleeding Varicose Veins in Banti's Syndrome, Ann. Surg. **126**:397 (Oct.) 1947.

5. Mayo, W. J.: Surgical Aspects of Diseases of Lymphoid Organs, with Special Reference to Spleen: With Statistical Report of Results Following Removal of Diseased Spleen in 530 Cases, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1929, vol. 21, p. 631.

6. Everson, T. C., and Cole, W. H.: Ligation of Splenic Artery in Patients with Portal Hypertension, Arch. Surg. **56**:153 (Feb.) 1948.

The operation, however, is a formidable one which carries a significant mortality and morbidity. This procedure has not been applied to any of the cases in the series under discussion, and in at least 2 instances complete obliteration of the upper part of the peritoneal cavity by adhesions from previous operations and fixation and thickening of the esophagus incident to repeated injections of sclerosing solutions would have rendered such an operation both difficult and dangerous, if not impossible.

B. Injection of Esophageal Varices: Although my colleagues and I have been gratified with the palliative results of injection of esophageal varices in many patients with advanced cirrhosis of the liver, we have observed no beneficial effects from this treatment in the younger patients with extrahepatic blocks of the portal system. Extensive injections of up to 27 cc. of sodium morrhuate have been given repeatedly, without any apparent diminution in the frequency or severity of the bleeding.

POSSIBLE EXPLANATION OF THE FAILURE OF CONVENTIONAL METHODS OF TREATMENT

When esophageal varices are large and of long duration, the walls of the veins are extremely thin and anastomotic channels have developed between the esophageal veins and those of the azygos system. These large channels are easily visible when the esophagus is exposed. Shunt operations which correct the portal hypertension cannot be expected to cause a regression of the decompensated esophageal veins whose communications with the azygos system are not protected by valves. Hence even if all communications with the portal system were cut or even if the pressure in the portal system were reduced to normal, the veins would still fill with blood and would still bleed if traumatized or ruptured by the increase of pressure incident to straining. Hence it would appear that the conventional indirect attacks on esophageal varices are of value only in early cases or prophylactically before the varicosities are well developed.

The direct method of attack by injection is subject to the same pitfalls as injection of varicose veins of the saphenous system. Although small channels may be obliterated successfully, larger ones either do not thrombose or are apt to recanalize. Certainly no benefit of long duration can be expected after injection of large veins.

Resection of the involved area of stomach and esophagus is a rational approach provided there is no tendency to reestablish anastomotic channels connecting with the portal system. Time alone will answer the question of the effectiveness of this form of treatment. The chief disadvantages are its risk and the attendant morbidity.

CASE REPORT (LIGATION OF ESOPHAGEAL VARICES)

The following case is reported to illustrate the difficulties of the problem of bleeding from esophageal varices.

History.—The patient was an unmarried woman 23 years of age. Hematemesis occurred at the age of 13, and the spleen was removed at the age of 16 for congestive splenomegaly. She had received injections of esophageal varices sixty times and transfusions one hundred and twenty-four times and had been admitted to the hospital sixty times. The stomach had been completely devascularized and transected and a small stump of cardia anastomosed to the jejunum, the distal nine-tenths of the stomach having been turned in and left in place. The vagus nerves had been divided. A subdiaphragmatic abscess on the left side had been drained. Resection of the esophagus and the gastric stump was rendered impossible by adhesions. The block was in the splenic vein and therefore portacaval anastomosis would have been of no value. Exsanguinating hemorrhages were occurring at intervals of two to four weeks. The only recognized procedure which had not been tried was mediastinal packing, but since the esophagus was completely detached from all veins of the portal system in which the pressure was increased, it seemed unlikely that the bleeding was coming from the portal side. It was assumed, therefore, that the bleeding was coming from communications with the azygos system, that the original cause of the varices had been corrected by devascularization of the stomach, gastric resection and splenectomy and that the only solution to the problem lay in a direct attack on the varices.

Technic.—With the patient under intratracheal anesthesia the seventh rib was resected and the esophagus exposed and isolated about 1 inch (2.5 cm.) above the diaphragm. A longitudinal incision 1 inch long was made in the esophagus, exposing the three large esophageal varices. Each of these veins was ligated with a surgical gut suture and obliterated downward as far as the stomach and upward for about 2 inches (5 cm.) by a continuous obliterating suture placed beneath the veins with a small curved needle. The pliability of the esophageal mucosa enables one to pull it into the field by traction on the last suture so that the varices of the lower third of the esophagus can be obliterated through a small incision. The esophagus was closed longitudinally with an inner layer of surgical gut sutures and an outer layer of interrupted silk, no attempt being made to invert the edges.

Results.—Ever since the devascularization of the stomach and vagotomy, which had been done over two years before, the patient had had severe epigastric pain after eating. This pain persisted intermittently. There was one slight episode of bleeding shortly after the varices were obliterated, which may have been due to slough. The patient was then entirely well for a year, had no more bleeding and returned to work. One and a half years after operation the pain recurred and was followed by bleeding. At this time a large ulcer was demonstrated in the small stump of the cardia. Medical and dietary management of the gastric ulcer was instituted. It is thought that the bleeding may be from the ulcer rather than from esophageal varices. Predisposing factors to the formation of the ulcer are the disturbed innervation and blood supply of the stomach and the fact that the stomach was transected but the antrum was not removed.

RATIONALE OF OBLITERATION OF ESOPHAGEAL VARICES

The operation of transesophageal ligation of esophageal varices is much like that of hemorrhoidectomy. The three large veins look exactly like the three large groups of hemorrhoids. It is hoped that after their

obliteration the control of bleeding will be as prolonged and as complete as after hemorrhoidectomy.

Although dilatation of the hemorrhoidal veins is probably due to increased pressure in the portal or hemorrhoidal system of veins, we do not approach this problem by attempting to reduce the pressure. Perhaps the pressure in the hemorrhoidal veins would be reduced by anastomosing the inferior mesenteric vein to a systemic vein, but if the hemorrhoids were large there is no doubt that they would continue to fill with blood and to bleed after trauma. The veins must be obliterated surgically or by injection of sclerosing solutions before the bleeding is controlled.

Although hemorrhoids occasionally may recur after removal, they are more apt to be the result of an incomplete operation than of

Data on 7 Cases of Bleeding Esophageal Varices

Case	1	2	3	4	5	6**	7
Age	23	13	13	30	21	13	20
Sex	F	F	M	M	M	M	F
Age at first bleeding	13	10	4	18	15	11	15
Age at splenectomy	16	11	5	19	21	14	10
Condition of liver *	N	N	N	N	N	..	N
Site of block †	S	S	P	S	S	..	S
Number of injections of varices	60	10	0	1	0	0	6
Devascularization of stomach and vagotomy	Yes	Yes	Yes	Yes	No	No	Yes
Total number of transfusions	124	50+	12+	?	42	312‡	100+
Number of hemorrhages per year before ligation	23	19	17	18	8	3	7
Number of months without bleeding since ligation	18§	14	12	13	3	1	2
Disappearance of varices on esophagoscopic examination	Yes	Yes	..	Yes	..	No	..
Disappearance of varices on roentgenograms	Yes	..	Yes	..	Yes	No	Yes

* N indicates normal.

** Patient had varices involving the lower half of the esophagus, all of which were not obliterated, and has bled once since operation.

† S indicates splenic vein and P portal vein.

‡ Patient had packing of mediastinum three years before operation, without benefit.

§ Eighteen months after operation patient bled from a large ulcer that developed in the stump of the stomach.

formation of new channels. Since a good hemorrhoidectomy usually affords permanent relief, no one gives serious consideration to the possibility of removing the rectum to control bleeding from hemorrhoids. If bleeding from esophageal varices can be as readily controlled by obliteration of these veins, it is hoped that resection of this area will be as unnecessary as removal of the rectum.

EXPERIENCE WITH LIGATION OF ESOPHAGEAL VARICES

We have treated 5 patients by devascularization of the stomach and obliteration of esophageal varices. Two more patients have been treated by obliteration of the varices unaccompanied with ligation of gastric vessels. All patients have had their spleens removed. All patients were

bleeding at frequent intervals prior to operation. From six to twenty-three months after operation there have been only 2 patients who have had recurrences of bleeding, and in 1 this appears to be from a clearly demonstrable gastric ulcer. This patient and 2 others subjected to devascularization of the stomach and vagotomy had severe gastric pain afterward, suggesting that the circulatory or trophic changes caused gastric ulceration. For this reason we have not devascularized the stomachs or performed vagotomies in our more recent cases but have merely ligated the veins of the cardia or have done nothing to the stomach.

The second person who has bled since operation was the patient in case 6 whose varices were so extensive that more than half of the esophagus was involved. Roentgenologic and esophagoscopic examinations show persistence of varices. The patient who has received over three hundred and twelve transfusions has bled once in seven months since operation as compared with every two weeks prior to operation.

SUMMARY

A group of 7 cases is reported in which the patients continued to bleed frequently and severely from esophageal varices in spite of conventional methods of treatment.

In this group of patients, all of whom had had splenectomy performed for congestive splenomegaly secondary to extrahepatic block of the splenic or portal vein, there have been only two recurrences of bleeding from seven months to two years after transesophageal ligation and obliteration of esophageal varices. One of the patients who bled has severe epigastric pain and a demonstrable gastric ulcer, which may be the source of the bleeding.

SPONTANEOUS CLOSURE OF THE PORTACAVAL ANASTOMOSIS IN THE EXPERIMENTAL ANIMAL

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AND
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THERE has been an interest in venous fistulas since 1877, when Eck [1] first suggested a technic for producing a portacaval anastomosis. Since that time many studies of the physiologic changes produced in animals by an Eck fistula have been reported.

Blalock,[2] Blakemore [3] and Whipple [4] have reported that a side to side portacaval fistula without obstruction of the portal vein will close, but to date no specific report of experimental work has been found in the literature. A similar fistula will remain patent in the typical animal with an Eck fistula, in which the portal vein is occluded.[5]

A few clinical cases have been reported in which there were recurrent gastrointestinal hemorrhages after the establishment of a portacaval fistula. It seems possible that this may be due to closure of the fistula in some instances. Many factors contribute to the maintenance of the patency of a venous fistula of this type. A physiologic need for a fistula exists when there is an obstruction of the portal vein. The marked difference in the pressure gradient between the portal vein and the vena cava in an obstruction of the portal vein will tend to keep such a fistula open. Complete obstruction of the portal vein, however, is undesirable clinically since all portal blood will by-pass the liver and

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From the Department of Surgery, Northwestern University Medical School. Aided by the Grunow Surgical Fund.

1. Eck, N. V.: The Ligature of the Portal Vein, Voyenno-med. J., 1877, cited by Linton, R. R.; Hardy, J. B., and Volwiler, W.: Surg., Gynec. & Obst. **87**: 129-144, 1948.

2. Blalock, A.: Use of Shunt or By-Pass Operations in the Treatment of Certain Circulatory Disorders, Including Portal Hypertension and Pulmonic Stenosis, Ann. Surg. **125**:129-141, 1947.

3. Blakemore, A. H.: The Operation of Portacaval Anastomosis: Indications, Report of Cases, New York State J. Med. **47**:479-485, 1947.

4. Whipple, G. E.: Personal communication cited by Whipple, A. O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies, Ann. Surg. **122**:449-475, 1945.

5. Freeman, S.: Personal communication to the authors.

deprive the body of the various hepatic functions already disturbed by disease.[6] Other factors which may contribute to closure of a fistula are thrombosis and infection. Therefore it was believed desirable to determine if a fistula in the experimental animal would remain patent without portal obstruction and if a technic could be developed to assure patency. It was for this reason that the present study was undertaken.

The technic described by Freeman [7] was used, except that the portal vein was not ligated. The abdomen of mongrel dogs weighing between 20 and 25 pounds (9 to 11 Kg.) was opened by a right subcostal incision with the animals under anesthesia induced by intra-

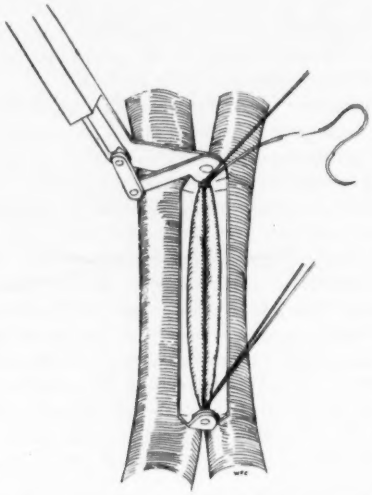

Fig. 1.—Longitudinal segments of portal vein and vena cava isolated by clamp after apposition of these veins with retention sutures. (After Freeman.[7])

venous injection of pentobarbital sodium. The duodenum and intestines were reflected to the left, revealing the portal vein and the inferior vena cava. After the portal vein was mobilized by dissection of its surrounding tissues, the portal vein and the vena cava were brought into side to side apposition with two sutures. The clamp was then applied, with occlusion of only a part of the lumen of the veins (fig. 1). The clamped

6. Linton, R. R.; Hardy, I. B., and Volwiler, W.: Portacaval Shunts in the Treatment of Portal Hypertension, Surg., Gynec. & Obst. **87**:129-144, 1948.

7. Freeman, S.: Studies on Eck Fistulas in Dogs: A Simple Technique for the Preparation of a Portacaval Anastomosis with the Aid of a Clamp, Surg., Gynec. & Obst. **87**:735-738, 1948.

portions of the vessels, isolated from the main flow of blood, could then be handled without the occurrence of hemorrhage and were opened longitudinally, their lateral portions being retracted by retention sutures. The superior apposition suture, which was left long, was utilized for the anastomosis (fig. 2). In all cases 00000 atraumatic Deknâtel silk was employed. After the death of the first and eighth animals, due to technical difficulties, no subsequent deaths occurred.

Side to side portacaval anastomosis by the suture method was the only procedure employed. Johns [8] recently pointed out the greater

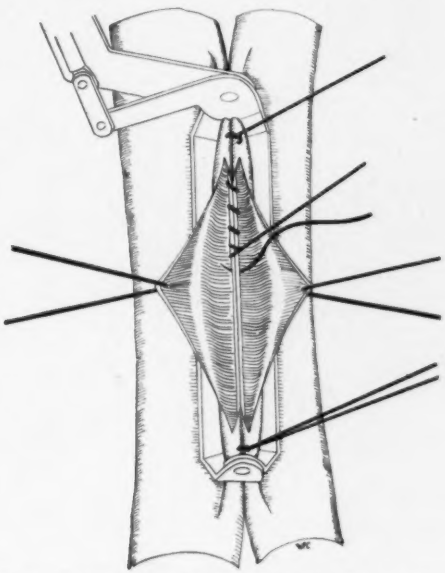

Fig. 2.—The isolated segments of portal vein and vena cava opened longitudinally. With the lateral portions of the veins retracted with sutures, the anastomosis is accomplished. (After Freeman.[7])

desirability of the suture over the nonsuture technic when tension on the suture line and bridging defects of the vessels are not encountered.

In the first series of 17 animals a continuous over and over suture was utilized. In this group the dogs were killed at periods of 5 to 68 days. Four of the 17 anastomoses were closed, and an additional 6 appeared to be closing. The fistulas had a linear slitlike ostium which became more ovoid with closure of the fistula.

8. Johns, T. N. P.: A Comparison of Suture and Nonsuture Methods for the Anastomosis of Veins, Surg., Gynec. & Obst. **84**:939-942, 1947.

Because intimal approximation is believed to be the ideal method for vascular anastomosis, it was felt that this method should also be investigated. Accordingly in the second series of 5 animals an eversion suture was employed. The dogs were killed in 40 to 89 days. Two of the 5 anastomoses were closed. This is similar to the results after the use of the over and over suture and confirms Blalock's [2] statement that eversion suture is impractical when working with veins.

Fig. 3.—A portacaval fistula which has closed. Dense fibrous tissue (center) replacing ostium. × Approximately 26.

Removal of a segment of vein wall in the performance of the anastomosis according to the procedure advocated by Bird [9] has the advantage of producing a more ovoid ostium of the fistula. Thus in a third series of 4 animals an elliptic segment of the vena cava was removed and the anastomosis performed with an over and over continuous suture. Our results to date support the contention of Bird,[9] and more recently of Riker,[10] that this method is superior in preventing closure of the fistula.

9. Bird, C. E.: Anastomosis of Veins, Surg., Gynec. & Obst. **42**:428-432, 1926.
10. Riker, W. L.: Personal communication to the authors.

One of these four fistulas was closed at 40 days, but the other three showed a widely patent ovoid ostium, with no evidence of an attempt at closure. In the one which had closed there was considerable induration, possibly signifying that infection may have played some part in the closure. This aspect of the problem is to be investigated more thoroughly.

The anastomosis was patent in all animals killed before 3 weeks, but the incidence of closure was moderately high in the 3 to 6 week time

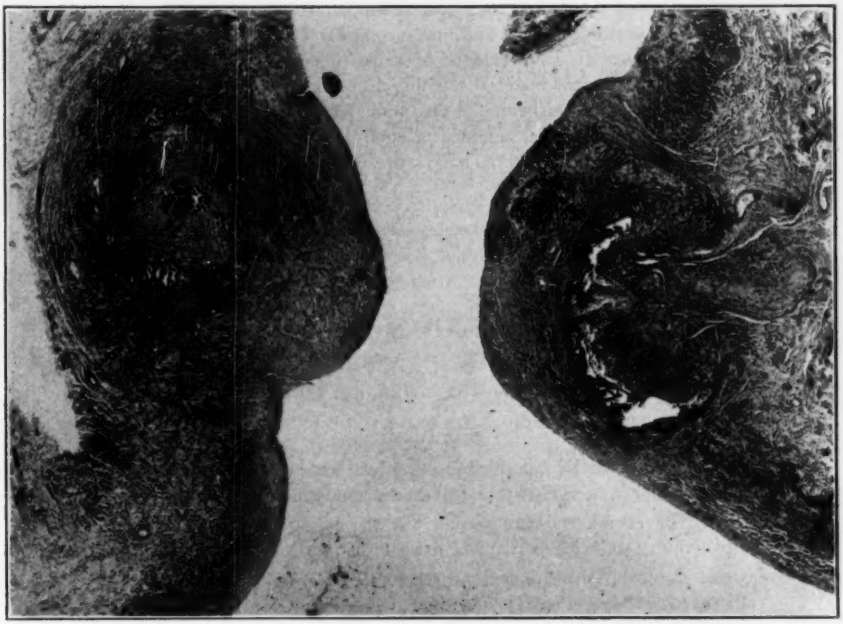

Fig. 4.—A patent portacaval fistula. There is subintimal fibrosis, with no thickening of the intima. Fibrosis present about suture material. × Approximately 26.

TABLE 1.—*Side to Side Portacaval Anastomosis*

Time Interval, Wk.	Closed	Patent
Under 3	0	5
Over 3	6	12*
Over 4	4	12
Over 5	5	11
Over 6	3	10

* Six closing.

interval (table 1). There was no significant variation between the over and over continuous suture and the everting suture with intimal apposition; approximately one third of all shunts were closed. Continuous suture with excision of a segment of the vena cava appears to produce more favorable results and is to be investigated further (table 2).

The gross appearance of the patent fistulas was similar in all cases. A smooth intimal covering was present over the line of suture, with the underlying suture material usually visible. Closure proceeded from the extremities of the fistula and was accompanied with a fibrous tissue reaction discernible grossly and microscopically (fig. 3). In two patent fistulas the ostiums were bridged by a fine fibrous band, produced, we believe, by the suture material catching a few fine shredded fibers of the divided vein wall. Thickening of the intima was not seen microscopically, but there was a variable amount of subintimal fibrosis (fig. 4). The reaction to the suture material was variable, and in some cases a marked

TABLE 2.—*Suture Technic in Portacaval Anastomosis*

	Dogs	Closed	Patent
Eversion	5	2	3
Continuous	17	4	13
Excised segment	4	1	3

inflammatory reaction was present. A small thrombus was present in only one case and was located on the intimal surface of the vena cava.

CONCLUSIONS

1. Approximately one third of portacaval anastomoses closed in from 3 to 6 weeks in normal experimental animals without portal obstruction.

2. The eversion suture technic for the anastomosis was no more effective in producing permanent fistulas than the over and over suture.

3. The excision of an elliptic segment of the wall of the vena cava appears to produce a more ovoid stoma. The number of animals in which this type of procedure was used is still not sufficient to warrant definite conclusions.

ADDENDUM

Since this paper was submitted for publication 13 anastomoses have been performed with excision of an elliptic segment of the vena cava. Of these, seven closed. Thus this technic is no more satisfactory than the simple over and over suture of simple linear incisions. Penicillin was administered postoperatively to four animals and was ineffective in preventing closure of the stoma in two.

EXPERIMENTAL USE OF PRESERVED ARTERIAL GRAFTS IN PORTACAVAL ANASTOMOSES

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IN RECENT years, through the work of such men as Whipple, Blakemore, Blalock and others,[1] the construction of an artificial connection between the portal and systemic venous circulations as originally described by Eck [2] has been accepted as a method of treatment of portal hypertension. In order to obtain a shunt of adequate size, most surgeons believe that either a direct portacaval or a splenorenal anastomosis should be performed. The type of operation utilized varies with the requirements of the specific case.

This investigation concerns itself with the situation in which the indications for the construction of the fistula are present but in which neither procedure is technically possible. Previous splenectomy, for all intents and purposes, precludes the construction of a splenorenal shunt. Though attempts have been made to isolate the stump of the splenic vein after removal of the spleen, these efforts generally have been

From the Department of Surgery, University of Illinois College of Medicine.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

1. Whipple, A. O.: The Rationale of Porta-Caval Anastomosis, Bull. New York Acad. Med. **22**:251, 1946. Blakemore, A. H., and Lord, J. W., Jr.: The Technic of Using Vitallium Tubes Establishing Porta-Caval Shunts for Portal Hypertension, Ann. Surg. **122**:476, 1945. Blakemore, A. H.: Indications for Porta-Caval Anastomosis: Analysis of Cases, Surg., Gynec. & Obst. **84**:645, 1947; The Porta-Caval Shunt in the Surgical Treatment of Portal Hypertension, Ann. Surg. **128**:825, 1948. Blalock, A.: The Use of Shunt or By-Pass Operations in the Treatment of Certain Circulatory Diseases, Including Portal Hypertension and Pulmonic Stenosis, ibid. **125**:129, 1947. Linton, R. R.; Hardy, I. B., and Volwiler, W.: Porta-Caval Shunts in the Treatment of Portal Hypertension: An Analysis of 15 Cases with Special Reference to the Suture Type of End-to-Side Splenorenal Anastomosis with Splenectomy and Preservation of the Kidney, Surg., Gynec. & Obst. **87**:129, 1948. Linton, R. R., and Hardy, I. B.: Surgery of Portal Hypertension: Porta-Caval Shunts and 2-Stage Method in a Poor-Risk Patient, J. Michigan M. Soc. **48**:1005, 1949. Rousselot, L. M.: Combined (One-Stage) Splenectomy and Porta-Caval Shunts in Portal Hypertension with Observations on Venous Shunts in a Postsplenectomy Patient with Recurring Hemorrhage, J. A. M. A. **140**:282, 1949.

2. Eck, N. V.: The Ligature of the Portal Vein, Voyenno-med. J. **130**:1, 1877.

fruitless. Similarly, a direct side to side portacaval anastomosis may be made technically impossible by the presence of an anomalous hepatic artery at the point where the fistula should be created, or the vessels may cross each other at such an angle that an adequate stoma cannot be obtained or, finally, as Dragstedt [3] has pointed out recently, mere distance separation of the vessels may prevent their anastomosis.

In these instances an end to side portacaval shunt might be considered, but this of course necessitates diverting the entire portal blood flow from what is generally an already damaged liver. Whipple [4] has demonstrated the undesirability of this procedure. In his experience, dogs with an Eck fistula were shown to be deficient in both plasma protein and hemoglobin production when compared with the control animals. The work of Smith Freeman [5] also demonstrates depression of dye clearance in dogs with Eck fistulas. However, if a vascular graft were placed between the portal vein and the vena cava, the anomalous situations could be obviated without complete interruption of the portal flow. The experiments reported here have been designed to test the practicality and value of such a procedure.

EXPERIMENTAL METHOD

Initially, the thoracic aorta was removed aseptically from donor dogs. Aortic segments were selected since it was hoped that, inasmuch as these had greater thickness than vein grafts, there would be a stability of the segment tending to promote continued patency of the stoma. After the vessel had been prepared by the removal of the areolar tissue and ligation of the intercostal arteries, it was divided into segments 2 cm. long and placed in a sterile solution containing 10 per cent homologous serum. The solution was prepared according to the technic described by Gross and his associates.[6] Basically, it is a modified Tyrode solution buffered to a p_H of 7.6 with sodium bicarbonate and containing also penicillin and streptomycin. The segments were stored from one to thirty days before use in rubber-capped 50 cc. Erlenmeyer flasks in a refrigerator with a temperature kept at from 1 to 4 C.

3. Dragstedt, L. R., in discussion of a paper by Dr. Ormond C. Julian at a meeting of the Chicago Surgical Society, February 1949.

4. Whipple, G. H.; Robscheit-Robbins, F. S., and Hawkins, W. B.: Eck Fistula Liver Subnormal in Producing Hemoglobin and Plasma Proteins on Diets Rich in Liver and Iron, J. Exper. Med. **81**:171, 1945.

5. Freeman, S.: Effect of Eck Fistula Formation, Simple Portal Obstruction and "Meat Intoxication" on Serum Phosphatase and Dye Clearance of Adult Dogs, Am. J. Physiol. **159**:351, 1949.

6. Peirce, E. C., II; Gross, R. E.; Bill, A. H., Jr., and Merrill, K., Jr.: Tissue-Culture Evaluation of Viability of Blood Vessels Stored by Refrigeration, Ann. Surg. **129**:333, 1949.

Mongrel dogs weighing from 10 to 17 Kg. were used. The animals were anesthetized with open drop ether, and a right rectus muscle-splitting incision was made. Adequate exposure of the portal vein and the vena cava was obtained through this incision when the intestines, covered with a moistened laparotomy pad, were retracted to the left and the liver, similarly covered, was retracted high under the costal margin after division of the hepatorenal ligament where necessary.

In the dog, the portal vein and the vena cava often lie in close proximity, lending themselves readily to a side to side anastomosis but presenting some technical problem when an attempt is made to insert a graft. However, in many instances lymph nodes as well as a tortuous

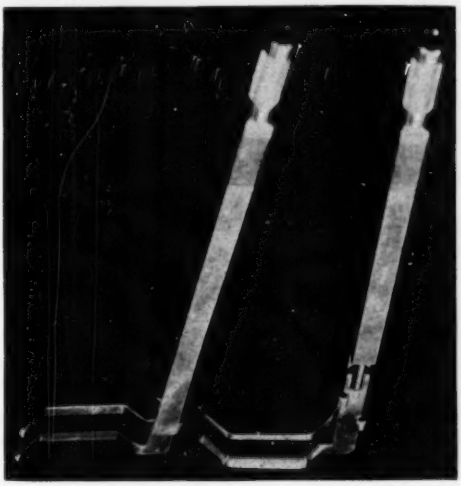

Fig. 1.—The clamp used during the construction of the anastomosis which allows occlusion of only a part of the vessel with minimal mobilization. Note the fine teeth along the grasping surfaces which hold the vessel firmly but do not damage the intima.

hepatic artery lie between the two vessels, creating the desired separation.

A specially designed set of clamps was utilized during the actual construction of the anastomosis (fig. 1). These instruments, which have been described elsewhere,[7] are constructed in mirror image, and fine teeth have been cut into the angled grasping surfaces. A firm but not damaging hold is taken in the vessel wall, and a segment of the vein can thus be occluded without interruption of the blood flow.

7. Southwick, H. W.: A Clamp for the Construction of Vascular Anastomoses, Arch. Surg. **60**:372 (Feb.) 1950.

Operative Technic.—The vena cava is grasped with smooth tissue forceps just on the medial side of the midline on the ventral surface. With the vessel under slight traction, a segment of the vein about 2 cm. long is isolated in one of the clamps. With the instrument closed, a small piece of the wall of the vein is excised, creating an elliptic opening from 0.8 to 1.4 cm. long corresponding to the diameter of the arterial graft.

One of the stored vessel segments is selected and cut to a length varying from 1 to 1.5 cm. depending on the distance between the two veins. One end of the graft segment is then sutured to the vena cava with the use of a continuous 00000 Deknatel silk suture with a curved minimal trauma needle (fig. 2). A simple continuous suture is used,

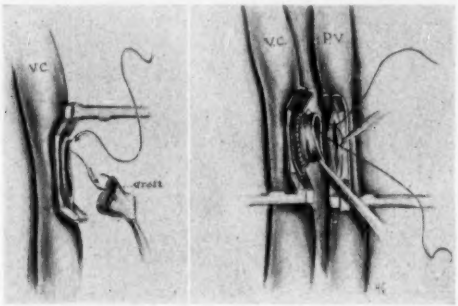

Fig. 2.—The anastomosis of the graft to the vena cava was performed first with the use of a simple continuous stitch. Though a piece was cut from the vena cava, creating an elliptic opening, only a slit was made in the portal vein because of its small caliber. In the left drawing suture passes from outside to inside of vena cava and from inside to outside of graft. At the right, anastomosis to vena cava is completed and initial stitch taken in portal vein.

for, while the everting stitch is theoretically superior, it has been shown that there is no significant difference in healing between the two methods.[8] Also, when dealing with small thin-walled vessels the continuous suture is technically much easier. Passing the suture from without inward through the vena cava and from the intimal surface outward through the graft allows the knot to be secured on the external surface. The suture is locked once at the distal angle when the stitch is reversed, so that the exact amount of tension can be maintained on the posterior suture line.

8. Sako, Y.; Chisholm, T. C.; Varco, R. L., and Merindino, K. A.: An Experimental Evaluation of Certain Methods of Suturing the Thoracic Aorta, Ann. Surg. **130**:363, 1949.

When this anastomosis is completed, a segment of the portal vein, cleared of peritoneal covering and areolar tissue, is grasped with the mirror image instrument. An incision is made in the wall of the vein with a scalpel, and the opening is enlarged to the proper dimensions with fine scissors. The small size of the portal vein in the dog makes it impractical to cut a piece from this vessel. The graft is then sutured to the portal vein with the same technic as the one employed for the anastomosis to the vena cava.

When the anastomosis is completed, the clamp is first loosened at the caval end, allowing blood to enter the arterial segment. Bleeding is generally minimal; both clamps are then opened, disconnected and

Results of Operation on 12 Dogs

Dog	Time Graft Preserved, Days	Time Graft in Place	Condition of Graft When Animal Was Killed	Comment
1728	3	1 wk.	Patent	.....
1275	2	2 wk.	Patent	.....
1609	8	3 wk.	Patent	.....
1693	1	4 wk.	Patent	Narrowing of stoma; collateral circulation developing
745	15	5 wk.	Patent	Narrowing of stoma; minute thrombus at caval suture line
1611	11	6 wk.	Occluded	Narrow slit remained at each anastomosis
1137	1	9 wk.	Occluded	Extensive collateral circulation
648	12	3 mo.	Occluded	Extensive collateral circulation
744	30	4 mo.	Occluded	Extensive collateral circulation
1733	2	4 wk.	.....	Animal still living
1735	1	4 wk.	.....	Animal still living
1763	2	5 wk.	.....	Animal still living

removed. At the conclusion of the operation a ligature is passed around the portal vein and the vessel occluded.

RESULTS

The operation has proved to be technically satisfactory in animals in which there was sufficient distance between the portal vein and the vena cava to permit insertion of the graft without kinking. This first series consists of 12 animals (table). All dogs which survived the first twelve hours postoperatively continued to live until killed. The greatest single cause of death during the immediate postoperative period was kinking of the graft resulting from the proximity of the two veins. These animals died with portal thrombosis.

The dogs were killed at varying times up to four months. All the specimens obtained one, two and three weeks postoperatively were patent and functioning. The suture lines in the specimens obtained

from these animals were smooth and covered with endothelium. There was no apparent narrowing of the stoma, and no significant collateral circulation was noted.

Animals killed after three weeks, however, were found to have a significant collateral circulation developing which was progressively more extensive the longer the grafts had been in place. Correlating with this was a narrowing of both the portal and the caval anastomotic

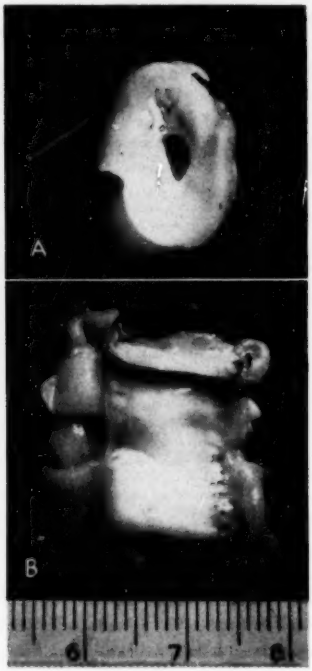

Fig. 3.—*A*, the vena caval anastomotic opening of the specimen removed at four weeks. Note the narrowing of the stoma which has taken place. *B*, the same specimen opened longitudinally. It is apparent that the narrowing is present only at the suture lines and that the graft itself is widely patent.

openings (fig. 3). This narrowing was first definitely apparent in specimens removed at four and five weeks. Although one small thrombus was noted at the caval suture line in the five week specimen (fig. 4), this was not the usual situation. The occluding process seemed not to be the result of thrombosis per se but rather to be associated with a gradual tissue proliferation at the suture line, with narrowing of

both openings. This was strikingly apparent in the graft removed at six weeks postoperatively, in which only a narrow slit existed at each end and which was occluded for all practical purposes. Even here, however, there was no thrombus in the graft itself. In all specimens removed subsequent to this, the anastomoses were closed, the grafts collapsed and a small organized thrombus was present within the segment. Three animals are still living, four and five weeks postoperatively, and will be examined at a later date.

While one of the thrombosed grafts had been preserved for thirty days (the longest any graft in the series was preserved before use), other thrombosed segments had been stored for as short a period as one day. On the other hand, specimens preserved as long as fifteen days were patent when examined. Gross and his associates have demon-

Fig. 4.—Specimen removed from an animal killed at five weeks. A small thrombus is present at the caval suture line on the left. The anastomotic openings here were narrowed, causing the wrinkling of the intimal surface seen in the lower part of the graft.

strated viability of the aortic segments preserved at least forty days in the manner used in these experiments. While viability can neither be affirmed nor denied, there was no correlation in the experiments under discussion between the length of time the graft was preserved before use and the ultimate patency of the anastomosis.

The specimens removed were also examined microscopically. The intima of the grafts appeared intact in the patent and more recently occluded specimens. Extensive medial degenerative changes were noted, however. Rather marked fibroblastic proliferation was present at the suture lines in the partially occluded specimens. In the nonfunctioning segments, the walls of the graft were collapsed and a small organized thrombus was present between the two surfaces.

COMMENT

The use of a vascular graft in the construction of a portacaval shunt is a technically feasible operative procedure in dogs when there is a definite separation between the two vessels. Such a situation would obviously exist were the use of a graft clinically indicated. However, preserved arterial segments were unsatisfactory when used for the graft in this experiment.

It has been noted previously [9] that if the anastomotic opening is too small the increased pressure will stimulate the development of collateral circulation, which is followed subsequently by closure of the lumen. However, when the opening is considered adequate, as in this experiment utilizing segments of thoracic aorta, the possibility of some other occluding factor arises. While preserved arterial grafts function satisfactorily in arterial circuits,[10] these homologous segments may cause sufficient reaction at the suture line in a slow venous current to favor a fibroblastic proliferation at this site which subsequently results in obliteration of the anastomosis. Animals are being prepared at the present time with the use of autologous vein grafts as well as fresh homologous arterial segments in order to help clarify these preliminary results.

SUMMARY

The use of a preserved arterial graft in the construction of a portacaval shunt is a technically feasible operative procedure in dogs. The operation as outlined could extend the clinical application of shunt procedures when the spleen has been removed and a side to side portacaval anastomosis is not technically possible. Preliminary studies indicate that in normal dogs, even with proximal ligation of the portal vein, preserved arterial grafts are unsatisfactory segments for use in this operation.

DISCUSSION

OF PAPERS BY DRS. CRILE, DOUGLAS AND WEHN, AND SOUTHWICK

DR. JACOB K. BERMAN, Indianapolis: I have been interested in this discussion because I think one of the first considerations is the production of an atrophic or portal cirrhosis of the liver which is comparable to the condition observed in man. We became interested in this problem, fortuitously, perhaps, after Poppe and DeOliveira used polythene film to wrap aneurysms and thereby stimulate fibroplasia. Later, Yeager and Cowley showed that the active ingredient in solvent

9. Freeman, S.: Studies on Eck Fistulas in Dogs: A Simple Technique for Preparation of a Porta-Caval Anastomosis with the Aid of a Clamp, Surg., Gynec. & Obst. **87**:735, 1948.

10. Gross, R. E.; Hurwitt, E. S.; Bill, A. H., Jr., and Pierce, E. C., II: Preliminary Observations on the Use of Human Arterial Grafts in the Treatment of Certain Cardiovascular Defects, New England J. Med. **239**:578, 1948.

cast polythene film was dicetyl phosphate. We obtained some dicetyl phosphate from the DuPont Company and found that it would go into solution in olive oil at body temperature. Then we injected 0.9 per cent solution under the adventitia of the aorta in dogs and noted that it produced an enormous amount of fibroplasia.

Stone and Murphy used polythene film surrounded by a metal band wrapped around the portal vein in an attempt to produce experimental cirrhosis of the liver in dogs. They found that they could produce cirrhosis of the liver which was associated with the production of adventitious plexuses of veins around the vena cava, the renal veins and the rectum but they could not produce esophageal varices.

Now I come to our present interest in this subject, particularly in the paper by Dr. Crile. We have recently used dicetyl phosphate, 0.9 per cent in olive oil, in an effort to produce cirrhosis of the liver, with the hope that we might derive some benefit from the substance in the treatment of esophageal varices. Although we did not produce esophageal varices in dogs, the slides I have to show you will demonstrate the reaction of this material in the few animals studied thus far.

(Slides) This points to the adventitious vein in the gastrohepatic omentum in a dog; this shows the plexus of veins in the left leaf of the diaphragm and this also shows a plexus of veins on the under surface of the liver.

(Slide) This is an illustration of the dicetyl phosphate injected around the portal vein about 2 cm. from the liver, and this is the portal vein within the substance of the liver, although the injection was not placed at this site. Note the enormous amount of fibroplasia that occurs in three and a half weeks after the injection.

(Slide) This is the upper end of the esophagus in the dog three and one-half weeks after injection, and this is the site of the injection of the solution around the esophagus as it emerges through the diaphragm.

We have not studied animals long enough to determine whether or not an obstruction of the esophagus would result after complete cicatrization had occurred. However, since the mucosa is not damaged by the procedure, we do not think that an irremediable stricture will develop.

This work is still in the early experimental stage, and I merely suggest it as another means of producing a progressive fibrosis and fibroplasia around blood vessels in an attempt to produce experimental portal cirrhosis of the liver and to control bleeding from esophageal varices.

DR. JOHN H. GRINDLAY, Rochester, Minn.: Portal "hypertension" is certainly not hypertension in the same sense as arterial hypertension. For one thing, the latter is expressed in millimeters of mercury and the former in millimeters of water. It seems to me, moreover, that the word "hypertension" emphasizes the wrong thing, that (by connotation) it give undue importance to whatever increase in pressure there may be and that it ignores the great increase in the size of portal vessels, especially the collateral vessels.

My colleagues and I have learned that the portal pressure of a dog at the time of laparotomy is a different thing from its portal pressure after recovery from operation. Usually, higher pressures are found when the dog is on his back and the abdomen is open, especially if there is traction or pressure on certain viscera or when the vacuum holding the liver against the diaphragm is destroyed. It is unfortunate that studies on portal hypertension in man are based on measurements obtained at laparotomy.

Dr. Volwiler, Dr. Bollman and I have just completed a study in which we found that portal pressure and inferior vena caval pressure of the normal dog after recovery from operation were about 12 and 0 cm. of water, respectively. Intrahepatic or

extrahepatic portal obstruction caused portal pressure to increase to 20 cm. (200 mm.) and a caval pressure of 12 cm. (120 mm.). The most impressive findings in portal obstruction, however, were the great number and the large diameters of the collateral vessels. It would appear that the surgical construction of one more collateral shunt could have little effect. Furthermore, the elevation of inferior caval pressure and the presence of enlarged anterior abdominal wall veins, similar to those seen in obstruction of the inferior vena cava, suggest that the inferior vena cava is already carrying its full burden of portal blood.

True esophageal varices do not occur in portal obstruction in the dog. What have been called varices are, in our experience, dilated paraesophageal veins and not dilated submucosal veins. I have suspected that the horizontal position of the dog might explain this and that true submucosal esophageal varices might be produced if the venous flow from the esophagus were partly obstructed. In a few dogs with portal obstruction I excised part of the azygos vein and applied a constriction to the superior vena cava; within a short time great enlargement of the submucosal veins occurred.

DR. ORMAND C. JULIAN, Chicago: I should like to comment briefly on the papers by Dr. Douglass and Dr. Southwick. The spontaneous closures of portacaval shunts in the experimental animal are depressing as reported by Dr. Douglass, and his results are similar to ours. We have found a high incidence of closure of a portacaval lateral anastomosis in the experimental animal when this is done with a clamp that includes both vessels. This high incidence is an indictment of the production of lateral anastomosis in man, and in 1 clinical case in our experience the closure of the anastomosis has been indicated by the resumption of bleeding.

I do not believe that this is altogether a hopeless situation. The work of Dr. Douglass, I am sure, is progressing now to the study of what happens if the portal system pressure is increased by ligation. We have some data on this point. The simple ligation of the portal vein on the liver side of the anastomosis does not increase the ability of the shunt to remain open. I think there is a reasonable explanation for this; that is, that such a ligation does not produce permanent portal hypertension in the dog. The portal vein pressure increases certainly for a time, but then the formation of portal-to-portal collaterals reduces the pressure again to normal. In man there is a different situation, because the portal hypertension is maintained even after the production of a large portacaval anastomosis at the time of surgery.

In reference to Dr. Southwick's paper, his method of placing an arterial graft between the portal vein and the vena cava would certainly be a useful tool in patients in whom the various situations that he mentioned obtain. In one of my cases on which he commented the distance between the two vessels was too great for an anastomosis to be done. In another the anomalous position of the hepatic artery prevented the two vessels from being brought together, and in the third case the angle between the vessels was too great to produce a large anastomosis.

In these 3 cases such a method of placing the graft between the two vessels would have been extremely useful. I am sure, though, from Dr. Southwick's experimental work, that the results would be disappointing unless in the future a fresh rather than a preserved graft proves to be of greater lasting ability. His clamp is of interest also because of its applicability in a splenorenal end to end anastomosis. We have used this clamp in 5 clinical cases, applying it, of course, to the renal vein; it gives one a tremendous security because of the teeth. No damage is done to the renal vein, and it makes exposure of more than the upper surface of the renal vein unnecessary. Technically, it is superior to other forms of clamps that I have seen for the production of a splenorenal anastomosis.

SURGICAL MANAGEMENT OF MEDIASTINAL TUMORS

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AND
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CHICAGO

WE WISH to present the case histories of 3 patients with mediastinal tumors on whom we have operated during the past six months and to point out some of the diagnostic and therapeutic problems encountered. It has been our teaching practice to identify these tumors at least in part by their position as determined by roentgenograms of the chest in the arbitrarily drawn divisions of the mediastinum. Thus we can generally state that the most commonly encountered tumor of the posterior mediastinum is the neurofibroma. Particularly is this true if we consider any circumscribed, rounded, solid mass discovered either in the course of a routine examination of the chest or in the investigation of more definite intrathoracic symptoms. That one should be prepared to find and deal with other tumors which in all their clinical features resemble neurofibromas is exemplified in our first case.

CASE 1.—Mrs. Mollie C., a 52 year old white woman, had been in excellent health until two years before her admission to the hospital. At that time there was the insidious onset of a dull ache in the lower right thoracic region. This pain became progressively worse. She consulted a physician, who advised her to lose weight. He had discovered the mediastinal mass but felt that weight reduction should come before surgical intervention. On a reduction diet, she lost 23 pounds (10.4 Kg.) and felt much better. Eight months prior to her admission, she had a recurrence of pain, which became progressively worse. At the time of her admission the pain was so severe that it was not completely controlled by rather large doses of opiates. She had no other symptoms referable to her chest. A cholecystectomy six years previously had relieved attacks of colicky pain which she had been having in the right upper quadrant of her abdomen. She had been informed as a child of a congenital heart murmur. Physical examination revealed a moderately obese woman who was obviously in severe pain. The heart was not enlarged. There was a long, loud, rough systolic murmur along the left sternal border. There were no other positive physical findings. Venous pressure and circulation times were normal. There was mild normocytic anemia. The urine was normal. An electrocardiogram revealed right bundle branch block. Roentgenograms of the chest showed a large circumscribed mass in the right side of the posterior mediastinum (fig. 1). Bronchoscopic examination was essentially noncontributory. At thoracotomy a firm, round,

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fixed mass 6 by 8 by 12 cm. occupied the right costovertebral gutter. Its coverings were intimately adherent to the lung, chest wall and surrounding tissue. The tumor could be dissected free everywhere except at the vertebra. The bone did not appear to be invaded, but the tumor seemed to arise from between the fifth and sixth and the sixth and seventh dorsal vertebrae. The tumor was cut across at this point and the large mass removed. The postoperative course was uneventful. Microscopic examination of the tumor showed immature hyalinized cartilage surrounding areas of myxomatous mucoid material (fig. 2). The final diagnosis was myxochondroma of the posterior mediastinum.

It is interesting to speculate whether this tumor arose from the cartilage of the intervertebral disks and whether earlier surgical intervention would have permitted complete removal. It is probable that the tumor will recur locally at a slow rate. Obviously the prognosis

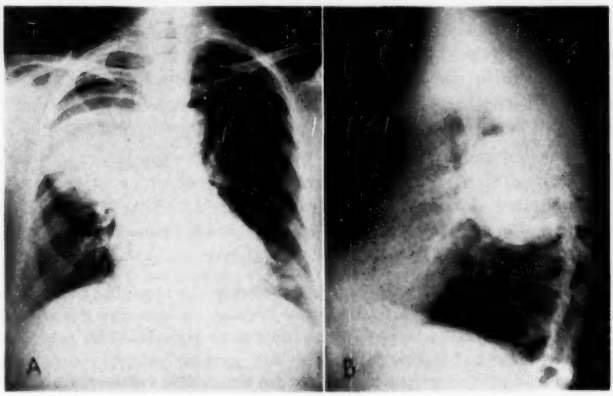

Fig. 1.—*A*, anteroposterior roentgenogram of the chest of a patient with a posterior mediastinal myxochondroma, possibly arising from intervertebral cartilage. *B*, lateral roentgenogram showing the posterior location of the same tumor.

was guarded, whereas with neurofibroma, unless malignant change has supervened, i. e., neurofibrosarcoma, cure can be expected. Since reports from the literature have called our attention also to the presence of intrathoracic meningiomas occurring in the posterior mediastinum, we have advisedly included them in our differential diagnosis. Needle aspiration of these rounded opacities in such accessible locations in our opinion is considered good surgical practice and may be the sole means of making a positive preoperative diagnosis. We feel, therefore, that it is worth while to point out that a growth which may have the characteristics of a posterior mediastinal neurofibroma preoperatively may prove at operation to be a tumor of a different nature and of an entirely different significance.

It has been our concept that the smooth, rounded, sometimes lobulated tumors of the anterior mediastinum must be strongly considered to be "dermoids" but may be the related epidermoids or ter-

Fig. 2.—Photomicrograph of the tumor seen in figure 1.

atomas, depending on the inclusion of elements of two, one or three germ layers in their microscopic pattern. Obviously many other varieties of new growths must be considered in a differential diagnosis of these anteriorly placed masses, as cases 2 and 3 make clear.

CASE 2.—Mrs. Mary C., referred in March 1949 by Dr. Joel Deuterman, of Elgin, Ill., was a 42 year old white woman who had had a nontoxic thyroid enlargement for eighteen years. Seven months prior to her admission she fell on the ice and fractured several ribs. A roentgenogram of the chest at that time revealed a large intrathoracic tumor (fig. 3). The patient was given a course of roentgen therapy to the tumor by her referring physician, without demonstrable change in its size. At the time she consulted us she was having no symptoms attributable to her chest. Physical examination was essentially noncontributory except that inspection and palpation of the neck disclosed a nodular enlargement of both left and right thyroid lobes. The right lobe could not be lifted above the sternal notch by the examiner's finger. The anteroposterior and lateral roentgenograms of the chest were interpreted by the roentgenologist as demonstrating an anterior mediastinal tumor. Our physical examination and analysis of the roentgenograms led us to believe that we were dealing with an intrathoracic goiter. We were struck by the idea, not then yet reported in the literature, that an examination of this lesion with

Fig. 3.—*A*, anteroposterior view of the chest in case 2. *B*, lateral view of the chest, demonstrating the anterior location of the intrathoracic shadow. There appears to be calcification in its upper portion.

radioactive iodine might establish positively and objectively its identity as thyroid tissue. We planned to await the establishment of this technic in our laboratories but were requested to proceed without it by the patient.

Through a collar incision somewhat longer than usual the thyroid was exposed. The superior thyroid arteries and veins, as well as the inferior thyroid arteries, were divided between clamps and secured. As planned beforehand, no attempt was made to expose the large veins as they coursed beneath the sternum into the thorax. Instead, the incision was converted into a Y shape and through the lower limb the sternum was split and separated by the use of a strong goiter retractor. It was gratifying to see the ease of delivery of the tumor and the safety with which the large, deep veins could be secured. At the conclusion of the removal, the sternal edges were approximated. We felt that tracheotomy offered the greatest safety against postoperative respiratory complication, considering the changed pressure relationships on the tracheal wall. The patient made a satisfactory recovery,

although her postoperative course was rather stormy. There was some evidence of parathyroid deficiency, which has responded to the usual medical regimen.

The point which we wish to emphasize is that a thyroid origin for anterior and other mediastinal tumors must be carefully considered. Once such an origin is suspected, radioactive iodine survey offers a method of confirming the diagnosis. Planned sternum splitting after the usual cervical dissection, but before uncontrollable hemorrhage from deep veins is encountered, makes a satisfying and safe method of removal of the larger intrathoracic goiter masses. Whereas tracheotomy need not be routine, it can be likened to draining the gallbladder bed after cholecystectomy, and, furthermore, in many instances it may be life-saving.

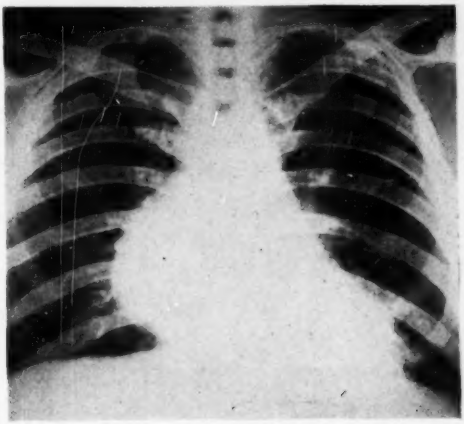

Fig. 4.—Anteroposterior view of the chest in case 3. A lateral roentgenogram did not clearly demonstrate the anterior location of the tumor.

Our most interesting and instructive patient with an anterior mediastinal tumor unfortunately was not treated successfully, but from his management we believe that we have learned an important lesson worth recording.

CASE 3.—S. M., a 41 year old white man, had been an outstanding athlete and had participated in sports both as a player and as a coach until four months before his admission to the hospital. In 1942 a routine roentgenogram of the chest taken elsewhere had demonstrated a tumor in the anterior mediastinum (fig. 4). Because he was asymptomatic, no specific therapy was initiated. Roentgenograms were made at repeated intervals, but because these failed to demonstrate any increase in size and because there was complete absence of symptoms, surgical intervention was not recommended. Four months prior to his first visit to us, he noticed a gradual onset

of generalized muscular weakness, dyspnea and diplopia. The symptoms were all slowly progressive, and at the time of his admission to the hospital he could scarcely walk three blocks and was unable to finish reading the daily newspaper. His symptoms were no worse at night than in the morning, but the slightest exertion produced marked fatigue, which could be relieved by a short period of rest. A

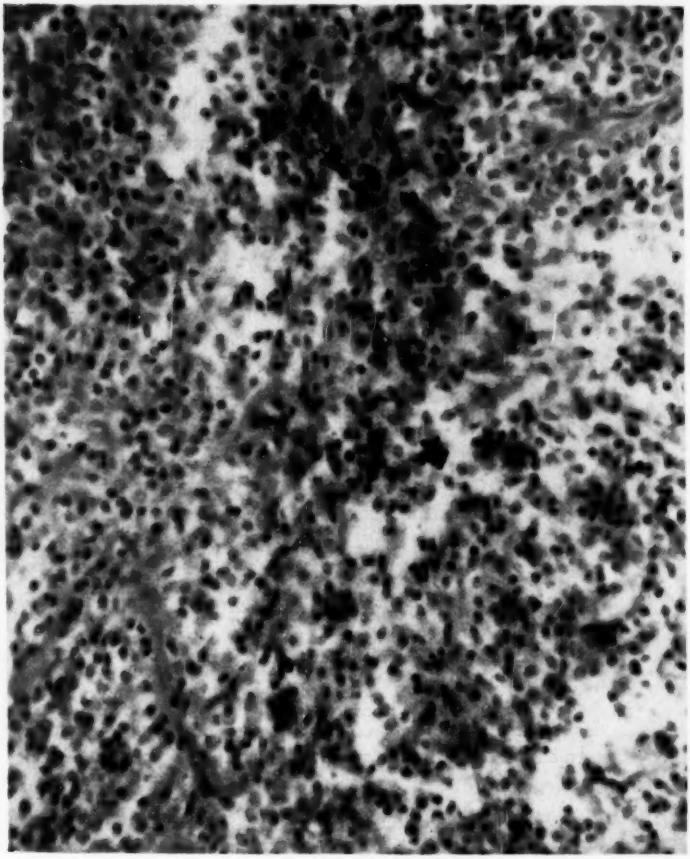

Fig. 5.—Photomicrograph of the tumor in case 3. The lymphoid nature of the tissue can be clearly seen.

complete study demonstrated mild diabetes, mild hypertension (blood pressure 160 systolic and 90 diastolic), early osteoporosis and a generalized muscular weakness including the eye muscles, which resulted in the diplopia. The question was raised whether this did not represent Cushing's syndrome due to thymic tumor.

However, myasthenia gravis was suspected, but a test dose of neostigmine seemed not to confirm this impression. The patient was taken to the surgery. On induction of anesthesia, a small dose of curare was given. He almost immediately complained of inability to breathe, and soon all respiratory movements stopped. He did not breathe at all for two hours and had to be maintained in a respirator for almost a day. On his recovery, a therapeutic trial of neostigmine was again given, without apparent benefit. A week later thoracotomy was performed. Eaton, in a personal communication, had warned of the dangers of curare in persons with myasthenia but had pointed out its value in carefully controlled test doses. None was given during the second anesthesia. A large anterior mediastinal tumor was found and immediate frozen section requested. The tumor was removed in its entirety except where it had extended behind the great vessels and along the left side of the trachea. It was impossible to resect this portion safely through our incision. The patient did not recover satisfactorily from the operative procedure. He had difficulty in breathing and was constantly dyspneic and cyanotic and had a rapid pulse. He died on the second postoperative day. Autopsy revealed some atelectasis of both lower pulmonary lobes. There was a small portion of tumor remaining in the region previously described. The adrenal and pituitary glands were normal. Microscopic section of the tumor (fig. 5) demonstrated that it was composed exclusively of lymphoid tissue and was certainly a thymoma. The nuclei of the reticuloendothelial cells varied considerably in shape. Many of the small cells resembled thymocytes actively proliferating, with mitotic figures being rather frequent. No Hassall's corpuscles could be demonstrated. We did not give this patient neostigmine postoperatively. Our frozen section had not been immediately interpreted as thymoma.

On the basis of our experience, we would recommend that curare should be assiduously avoided as an adjunct agent in anesthesia for anterior mediastinal tumors, unless a test dose has been given preoperatively by a competent clinician who knows proper dosage levels so as to administer the drug safely. Secondly, frozen section should be routinely made and thymoma suspected. The symptoms of myasthenia gravis may be latent. Thirdly, neostigmine can be given preoperatively and postoperatively without harm and may be lifesaving in case the precautions mentioned have not been taken.

SUMMARY

We have presented the case histories of 3 patients with varied mediastinal tumors and have set down the points in their surgical management which to us make them worthy of recording. The other oft-repeated warnings in favor of early surgical intervention should of course be heeded.

DIFFERENTIATION OF CONGENITAL CYSTS OF THE LUNG AND THOSE FOLLOWING STAPHYLOCOCCIC PNEUMONIA

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OUT OF the confusion of "cystic disease of the lungs" there has gradually evolved a definite division of lung cysts into those that are congenital and those that are acquired. Differentiation into those two types is vital since the prognosis and treatment of the two groups are not at all the same.

In dealing with infants and young children, we have found some difficulties in the past in differentiating cystlike cavities occurring in the lung fields after acute respiratory infections (usually staphylococcic pneumonia) from true congenital cysts. That we have not been alone in our confusion is witnessed by the fact that occasional lesions reported in the literature as congenital cysts have all the characteristics of post-infectious "pneumatoceles."

CONGENITAL CYSTS OF THE LUNG

In a review of the cases of "congenital lung cysts" observed at the Children's Memorial Hospital, 12 were found in the records of the past fifteen years. Only 6 of these were definitely proved to be cases of true congenital lung cysts at operation or autopsy. These are summarized in table 1. Three of the 12 lesions proved to be pneumatoceles or acquired cysts following staphylococcic pneumonia, and 3 could not definitely be proved pneumatoceles but appeared to be. Two cases illustrative of true congenital lung cysts are presented in detail.

CASE 1 (table 1).—L. H., a 5 week old white boy, was admitted to the hospital on March 31, 1941, because of a nonproductive cough since birth. He had had no respiratory infections. Roentgenograms showed a large, multiloculated cyst filling the lower two thirds of the right pleural cavity and displacing the mediastinum to the left (fig. 1*A*). Operation was refused, and the child was observed over a six year period. During this time he had no unusual number of respiratory infections

From the Department of Surgery, Children's Memorial Hospital.

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or other specific symptoms referable to the cyst. However, he was anemic and underdeveloped. Roentgen examination showed that the cyst had grown in direct ratio to the growth of the lung (fig. 1 *B*).

Thoracotomy was done on Aug. 13, 1947, and the right middle lobe found to be the site of a huge cyst. After collapse by aspiration the cavity quickly filled with air via its bronchial connection. The middle lobe was resected. The child made an uneventful recovery.

Microscopic examination revealed a typical congenital lung cyst lined by cuboidal epithelium.

It is rare for a true lung cyst to remain innocuous for so long a period. The usual history in a case of lung cyst, as illustrated in case 3 (table 1), is that of empyema, drainage, recovery, reinfection and repeated drainage until finally the cyst is recognized and removed. Differentiation of empyema from lung cyst is well discussed by Maier and Haight.[1]

TABLE 1.—*Proved Congenital Lung Cysts*

Case	Age	Clinical Manifestations	Roentgen Findings	Treatment	Results
1	5 wk.	Cough since birth	Large cyst in right chest with mediastinal shift	Lobectomy	Recovery
2	5 days	Cyanosis and dyspnea	Large cyst in right chest with marked mediastinal shift	Lobectomy	Recovery
3	8 yr.	Cough and fever; "empyema"	Density in left lower lobe	1. Drained as empyema 2. Thoracoplasty 3. Lobectomy	Recovery
4	6 mo.	Dyspnea since birth and cough	Multiple cysts in entire right chest	1. Needle aspiration 2. Pneumonectomy	Recovery
5	6 mo.	"Feeding problem"	Multiple cysts in entire right chest with mediastinal shift	Lobectomy	Recovery
6	4 yr.	Vomiting, diarrhea and fever; temperature, 106 F.	No roentgen examination	None	Died 2 hr. after admission; autopsy—incidental cyst of left upper lobe

CASE 2 (table 1).—R. K., a 5 day old white male infant, was brought to the hospital on Nov. 15, 1949, with the history of regurgitation of feedings and cyanosis on the fourth day of life. Even under oxygen the child was dyspneic and cyanotic. Roentgenograms showed large, multiple, cystic cavities filling the right side of the chest and pushing the heart to the left (fig. 2 *A*). The left lung appeared atelectatic. Four hours after his admission the child was operated on as an emergency.

When the chest was opened through the right sixth interspace, the tense, lobulated cyst bulged out through the wound. As the cyst was aspirated and collapsed, the infant stopped breathing, presumably because of the sudden change in intrapleural pressure. Only the quick insertion of an intratracheal tube and artificial respiration saved his life. The cyst involved the entire lower lobe of the right lung. The middle and upper lobes were atelectatic but apparently not cystic. The lower lobe was removed. Complete expansion of the upper and middle lobes revealed that they were far smaller than normal; in fact, they could be expanded to fill only the upper third of the chest cavity. A de Pezzer catheter was inserted through the

1. Maier, H. C., and Haight, C.: Large Infected Solitary Cysts Simulating Empyema, J. Thoracic Surg. **9**:471 (June) 1940.

seventh interspace for drainage and the chest closed snugly. On return to the room, the catheter was connected to an underwater seal with continuous slight negative suction.

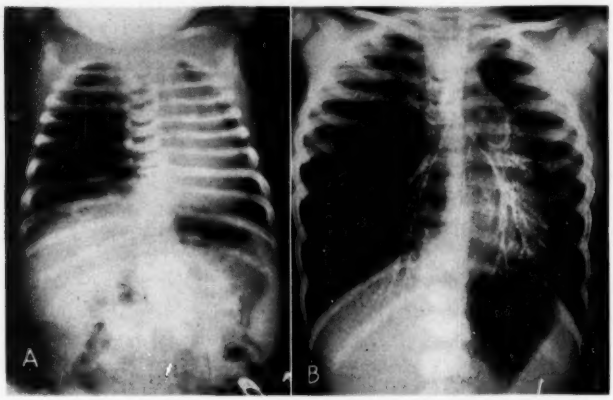

Fig. 1 (case 1).—*A*, congenital cyst of the right lung in a 5 week old infant. *B*, the same cyst at the age of 6 years. The cyst has grown in direct ratio to the growth of the lung.

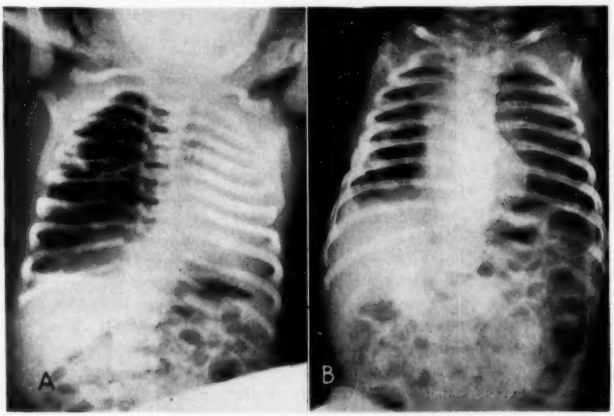

Fig. 2 (case 2).—*A*, multiloculated cyst of the right lung in a 5 day old infant. The heart is pushed far to the left. *B*, six weeks after removal of the lower lobe the right side of the chest is well aerated but the heart is now drawn to the right (see text).

Recovery was uneventful. Six weeks later roentgen examination showed the right side of the chest well aerated and the heart drawn to the right (fig. 2 *B*). The infant is clinically well.

The upper portion of the removed lobe contained a large loculated cyst and many smaller cavities. Microscopic examination showed that the main cyst as well as the multiple cavities were lined with low columnar or cuboidal epithelium.

These two cases are illustrative of rather typical congenital lung cysts. The first was discovered at the age of 5 weeks but was temporized with for over six years. Fortunately no serious complications occurred during that period. The second patient, we believe, is the youngest to have undergone successfully a lobectomy for lung cyst. Fisher [2] in 1943 reported a patient operated on at 1 month of age. Gross [3] in 1946 recorded successful operation on a 3 week old infant. Burnett and Caswell [4] reported lobectomy on a 15 day old infant in 1948.

Pathologic Process.—The concept of congenital cysts of the lung has gradually been clarified since the work of Anspach and Wolman.[5] It is now generally accepted that congenital lung cysts are formed during embryonic development. It is surmised that during the growth and development of the bronchial buds intermediate portions of the lumens may be blocked off, allowing peripheral formation of cystic cavities lined with bronchial structures and filled with secretions. When the obstructed bronchial lumen is forced open, the fluid may be evacuated and be replaced by air. If the bronchial opening is large, the cyst remains the same size. If it is narrow and tortuous, a check-valve mechanism may allow the cyst to balloon up under tension, as in case 2.

To be classified as congenital, the cyst must be lined with bronchial type epithelium, usually columnar and often ciliated. The walls may contain smooth muscle, cartilage and bronchial glands. Certain authorities who believe that congenital cysts are extremely rare argue that acquired cavities may gradually become lined by epithelium from the bronchus. This would seem an unlikely possibility in infants.

Treatment.—Early operation on congenital lung cysts appears to be the treatment of choice. In case 2 operation was a lifesaving procedure. Single aspirations of tension cysts are dangerous and of temporary benefit only. Such cysts rapidly refill,[1] and there is danger of leakage into the pleural cavity, with consequent tension pneumothorax. If needle aspiration is done, constant attendance is necessary with preparations for

2. Fisher, C. C.; Tropea, F., Jr., and Bailey, C. P.: Congenital Cysts of the Lung: Infant Treated by Lobectomy with Recovery, J. Pediat. **23**:219 (Aug.) 1943.

3. Gross, R. E.: Congenital Cystic Disease of the Lung, Ann. Surg. **123**:229 (Feb.) 1947.

4. Burnett, W. E., and Caswell, H. T.: Lobectomy for Pulmonary Cysts in 15-Day-Old Infant with Recovery, Surgery **23**:84 (Jan.) 1948.

5. Anspach, W. E., and Wolman, I. J.: Large Pulmonary Air Cysts of Infancy, with Special Reference to Pathogenesis and Diagnosis, Surg., Gynec. & Obst. **56**:635 (March) 1933.

relief of recurrent respiratory embarrassment until operation can be performed. Continuous catheter drainage with constant suction may be used as an emergency measure, but removal of the cyst-containing portion of the lung is the only definitive treatment. An argument in favor of early operation on congenital cysts is the avoidance of the frequent and often severe complications such as repeated infection, ballooning of a cyst with shift of the mediastinum and respiratory distress and rupture of the cyst with resultant tension pneumothorax. Lobectomy is simple in infants because adhesions have not had a chance to form. In older patients pneumonectomy must be substituted occasionally for a lobectomy because infection has obliterated landmarks and normal planes of cleavage.

Most forms of treatment have given way to surgical removal of the epithelium-lined structure. Enucleation of a cyst is occasionally possible. At times only a segment of lung need be removed. Most commonly the disease is limited to one lobe and lobectomy is curative. Pneumonectomy is sometimes necessary to remove all the diseased area. If the disease is widespread throughout both lungs, treatment must be determined according to the merits of the case.

STAPHYLOCOCCIC PNEUMONIA

Differentiation of a true lung cyst from the acquired type is of primary importance because the former will not disappear spontaneously while the latter may. We have been impressed with the frequency of appearance of round radiolucent areas in the infected portions of lungs during the course of staphylococcic pneumonia. The significance of such roentgen findings was forcibly impressed on us in the following case.

Case 7 (table 2).—R. B., a female infant 15 days old, was brought to the hospital on March 29, 1947, with a history of coughing for one week. For three days she had been dyspneic and for one day was unable to retain any feedings.

The rectal temperature was 99.6 F. The white blood cell count was 17,400, with 56 per cent polymorphonuclear leukocytes. She was slightly cyanotic and dyspneic. Tympany and diminished breath sounds were found over the entire left side of the chest. Roentgenograms showed homogeneous density of the left lung field except for a collection of air-containing pockets above the lateral half of the left region of the diaphragm (fig. 3). The surgeon, pediatricians and roentgenologist all interpreted this to be a diaphragmatic hernia. To be doubly sure, chloriodized oil (iodochlorol®) was given orally and follow-up roentgenograms taken. The opaque material entered the colon in a few hours, but was not shown in the chest. So convincing was the original diagnosis that this evidence was minimized.

The day after the patient's admission to the hospital the abdomen was opened through a left rectus incision for repair of the diaphragmatic defect. The diaphragm was painfully normal, and the abdomen was promptly closed. The child made a surprisingly rapid recovery and was discharged twelve days after operation with a diagnosis of congenital lung cysts.

Nine days later the child reentered the hospital with pyopneumothorax. The rectal temperature was still normal, but the white blood cell count was 25,000. Three thoracenteses were done, with injection of penicillin into the chest, but without improvement. Rib resection with open drainage was necessary. Cultures of the empyema fluid revealed Staphylococcus aureus.

In three weeks the cavity was obliterated. The drainage tube was removed and the child sent home in good health. Roentgenograms of the lungs were entirely normal.

In retrospect, it is easy to see that staphylococcic pneumonia must have developed during the second week of life. Air pockets developed

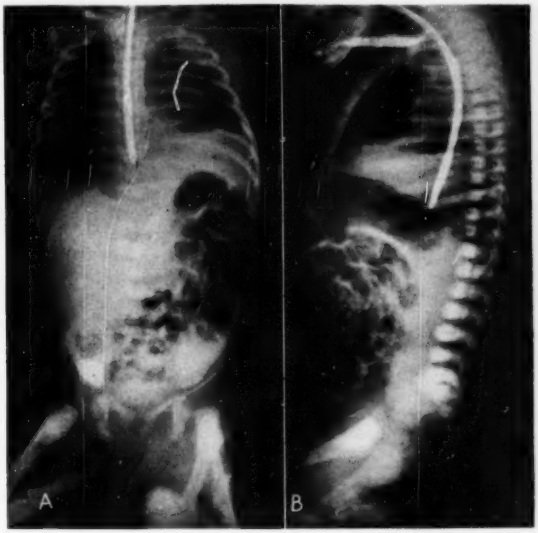

Fig. 3 (case 7).—*A*, pneumatoceles in the left side of the chest in a 15 day old infant with staphylococcic pneumonia. *B*, lateral view, taken at the same time as the anteroposterior view, shows a large accumulation of air in the chest. The negative shadows seemingly extending from the abdomen through the diaphragm into the chest misguided us into making a diagnosis of diaphragmatic hernia.

in the periphery of the consolidated lung, eventually ruptured and produced a pyopneumothorax. Our mistake is not unique. A patient reported by Burnett and Caswell [4] was operated on first for diaphragmatic hernia and later for congenital lung cysts. A visiting surgeon from North Carolina this year was comforted by our stupidity. He had recently made exactly the same error.

That the opposite mistake can happen is also possible. Cases have been reported in which diaphragmatic hernias have simulated lung cysts.

A diaphragmatic hernia on the right side recently operated on by us so closely resembled a lung cyst that roentgen studies after iodochlorol® was given by mouth were necessary before a definite diagnosis could be made.

The difficulty of differentiating true lung cysts from those following staphylococcic pneumonia is illustrated by the following cases:

TABLE 2.—*Lung "Cysts" Following Staphylococcic Pneumonia*

Case	Age	History and Clinical Findings	Initial Roentgen Findings	Complications	Culture	Results
7	15 days	Dyspnea, fever 3 days; dulness, diminished breath sounds over entire left chest; temperature, 102 F.	Homogeneous clouding of left hemithorax with air pockets above diaphragm	1. Operated on for diaphragmatic hernia 2. Pyopneumothorax	Staph. aureus (empyema fluid)	Complete recovery
8	9 wk.	History of pneumonia 6 wk. before appearance of lung "cysts"; temperature, 99.6 F.	Entire right hemithorax filled with air pockets	Residual pneumatoceles	None	Died of other causes; cysts disappeared
9	5 wk.	Cough, fever 10 days; dulness over right chest; temperature, 100.4 F.	Consolidation in right lung with air pocket	Residual air pocket—probable pneumatocele	Staph. aureus (thoracentesis)	No follow-up
10	2½ mo.	Cough, fever 1 day; consolidation of right lower lobe; temperature, 102.4 F.	Consolidation with a few "air bubbles"	Tension pyopneumothorax (closed drainage)	Staph. aureus (empyema fluid)	Complete recovery
11	4 mo.	Cough, fever 1 week; right lower lobe consolidation; temperature, 103.6 F.	Consolidation of right lower lobe	Residual pneumatocele	Staph. aureus (pharyngeal culture)	Complete recovery
12	4 mo.	Cough and fever 3 days; right lower lobe consolidation; temperature, 105.4 F.	Cystlike cavities and empyema	No treatment required; no residual findings	Staph. aureus (pharyngeal culture)	Complete recovery
13	6 mo.	High fever 2 days; right lower lobe consolidation; temperature, 103.8 F.	Consolidation in right lower lobe	Loculated pyopneumothorax	Staph. aureus (empyema fluid)	Complete recovery
14	1 yr.	Fever and dyspnea 1 day; right lower lobe consolidation; temperature, 104 F.	Consolidation of right lower lobe	Loculated pyopneumothorax	Staph. aureus (empyema fluid)	Complete recovery
15	7 mo.	Fever, cough 2 days; right lower lobe consolidation; temperature, 105.2 F.	Clouding of entire right lung field	Empyema with air pockets in lung	None	Complete recovery

CASE 8 (table 2).—V. R., a 9 week old white female infant, was brought to the hospital on April 20, 1947, with the original diagnosis of congenital lung cyst. The history revealed that at 2 weeks of age high fever, dyspnea and cyanosis had developed and she was taken to another hospital. Roentgenographic studies revealed lobular consolidation of almost the entire right lung, diagnosed as pneumonia (fig. 4 *A*). She had been extremely ill, requiring treatment with oxygen, penicillin and sulfonamides. After three weeks she was clinically improved; however, roentgenograms taken before her discharge from the hospital showed what was interpreted as congenital lung cysts.

On her admission to this hospital the temperature, white blood cell count and general physical condition were normal. Roentgenograms showed the right hemithorax filled with multiple cystlike cavities (fig. 4 *B*). Bronchoscopy revealed no unusual findings. Roentgen studies made five months later showed that all but one

cyst in the upper portion of the right lung had disappeared (fig. 4 *C*). About this time a diagnosis of amaurotic familial idiocy was made by Dr. Joseph K. Calvin. The child lived to the age of 18 months and died of terminal pneumonia. Autopsy, performed at Michael Reese Hospital, revealed no cystic cavities in the lungs.

Case 9 (table 2).—P. M., a 5 week old female infant, entered the hospital on June 22, 1936, with the history of a "head cold" for two weeks followed by cough and wheezing respirations for ten days. The rectal temperature was 100.4 F. The white blood cell count was 40,450, with 86 per cent polymorphonuclear leukocytes. Dulness and diminished breath sounds were found over the right side of the chest. Roentgenograms showed homogeneous density in the right middle portion of the chest, with a tiny "air bubble" at the level of the third rib (fig. 5 *A*). Twenty cubic centimeters of thick brownish fluid was aspirated, which on direct smear and on culture showed only Staph. aureus. Over the period of one month the clouding of the lung fields gradually disappeared spontaneously and the child was clinically well. Before her discharge, on July 24, roentgenograms shows a moderate-sized residual

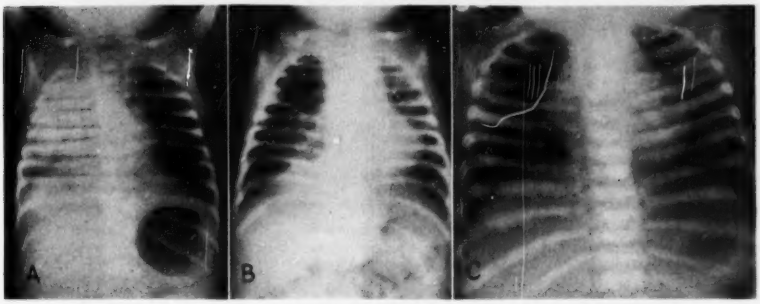

Fig. 4 (case 8).—*A*, pneumonia, presumably staphylococcic, in a 2 week old infant. *B*, multiple cystic cavities in the right lung at the age of 9 weeks. *C*, at the age of 7 months all but one poorly outlined cyst in the upper lobe had disappeared. Patient died at the age of 18 months of amaurotic familial idiocy. Postmortem examination revealed no cysts in the lung.

cystic area in the lower portion of the right lung (fig. 5 *B*). Six years later she was seen in the outpatient department for another condition and had apparently been healthy. Unfortunately, roentgenographic studies of the chest were not made.

The three questionable cases of lung cyst referred to on the first page of this paper are of interest because a definite diagnosis has been impossible. One patient cannot be traced. In the second, a 5 year old boy, a symptomless cyst, 3 cm. in diameter, was found in the right lung on routine roentgen examination of the chest. During infancy the child had had frequent infections of the upper respiratory tract and two questionable episodes of pneumonia. The cyst is symptomless, and no treatment is being advised. The third patient is an infant who was severely ill with diarrhea, bilateral otitis media and questionable pneumonia at the age of 4 months. During the course of this illness a

roentgenogram of the chest revealed a cyst below the hilus of the right lung (fig. 6 *A*). One and a half years later the child is perfectly well and the cyst has disappeared (fig. 6 *B*). This cyst was almost certainly a

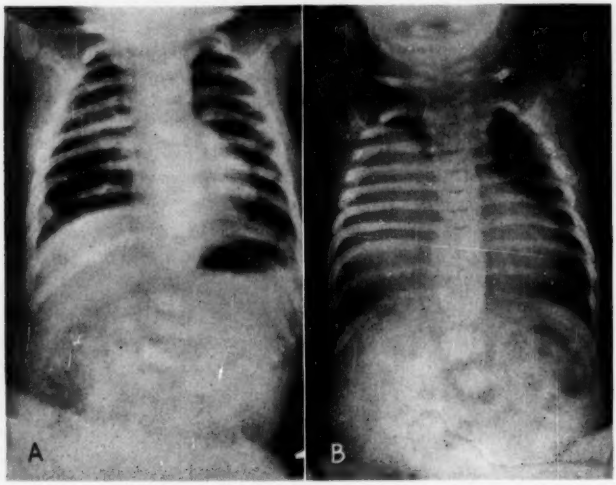

Fig. 5 (case 9).—*A*, staphylococcic pneumonia in a 5 week old infant. A tiny cyst can be seen below the third rib on the right side. *B*, one month later a typical pneumatocele is seen in the clearing lung.

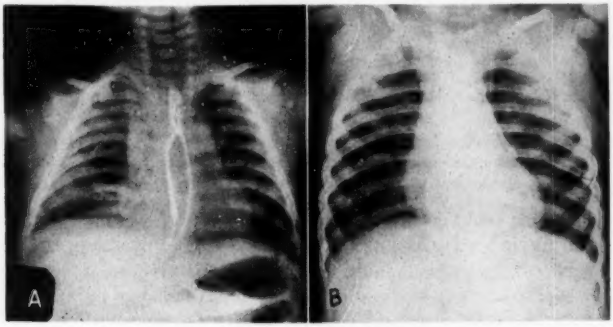

Fig. 6.—*A*, typical pneumatocele in a 4 month old baby severely ill with bilateral otitis media, diarrhea and questionable pneumonia. *B*, one and a half years later the cyst has disappeared spontaneously.

pneumatocele because roentgenograms of the chest of the child taken at the age of 3 days showed normal lungs.

Increasing emphasis has been placed on the occurrence of staphylococcic pneumonia in infancy, especially since the widespread use of sulfonamides and antibiotics has decreased the number of pneumococcic infections. Benward [6] stressed the fact that 75 per cent of the cases of staphylococcic pneumonia involve children under 1 year of age. Forbes [7] reported that 91 per cent of their cases of empyema in infants under 6 months of age were due to the staphylococcus.

The clinical picture is usually striking because of the severe toxicity of the patient. The fever is often rather high and the breathing rapid and labored. There is usually pallid cyanosis. Meningismus and convulsions are not uncommon. Physical examination will show dulness, decreased breath sounds and rales over the involved lung. Initial roentgen examination usually shows the consolidation stage of the disease. Repeated roentgenograms during the illness will often reveal discrete, round radiolucent areas in the consolidated lung parenchyma. Empyema or pneumothorax frequently follows. Tension pneumothorax may follow rupture of a cyst or bleb and require emergency aspiration and closed drainage, as in case 3.

To understand the cause of these pneumatoceles, one must go back to the pathologic and physiologic processes of the original infection. Staphylococcic invasion is by way of the bronchi and is often preceded by or accompanied with viral infection (Michael).[8] Peribronchial consolidation is usually followed by suppuration in the form of multiple tiny abscess cavities. Such cavities may break into the pleural cavity and cause empyema. If such an abscess is connected with an open bronchus and ruptures into the pleural cavity, a pyopneumothorax will result. If an abscess in the lung breaks into and evacuates through a bronchus, a small air-containing cavity may result. The small inflamed bronchus entering this cavity may allow entry of air but not egress because of the check-valve mechanism formed by the combination of bronchial occlusion from edema and normal expiratory constriction of the bronchus. Gradually the cavity may enlarge, displacing the adjacent lung. Such cystlike spaces may remain for long periods after the infant has recovered from pneumonia. They may vary greatly in size, occasionally ballooning up to alarming proportions. Suddenly the pneumatocele may disappear

6. Benward, J. H.: Staphylococcus Pneumonia and Empyema, Journal Lancet **67**:434 (Dec.) 1947.

7. Forbes, G. B.: Diagnosis and Management of Severe Infections in Infants and Children: A Review of Experiences Since the Introduction of Sulfonamide Therapy: V. Staphylococcal Empyema: The Importance of Pyopneumothorax as a Complication, J. Pediat. **29**:45 (July) 1946.

8. Michael, M., Jr.: Staphylococcus Aureus Pneumonia with Special Reference to Its Occurrence as Complication of Influenza, J. A. M. A. **118**:869 (March 14) 1942.

entirely because of loss of the valvular mechanism in the bronchus and reexpansion of the surrounding lung. They rarely become infected.

Treatment.—Cystlike areas in the lung discovered during or subsequent to a pulmonary infection in infants, usually staphylococcic pneumonia, rarely require specific treatment. The vast majority will disappear spontaneously. Only if a pneumatocele reaches such proportions that it embarrasses respiration or threatens to rupture and form a tension pneumothorax is active treatment indicated. Head and Avery [9] have outlined a satisfactory method of treatment for pneumatocele in adults. They employ the Monaldi technic of producing pleural adhesions over the site to be punctured and then insert a catheter which is kept on constant negative pressure. The cystic cavity collapses, the surrounding lung expands and the walls heal together.

COMMENT

The primary causes of radiolucent areas in the lungs in infants are congenital lung cysts and acquired lung cysts or pneumatoceles. Pierce [10] and Caffey [11] and, more recently, Almklov and Hatoff [12] have championed the idea that the majority of "cysts of the lungs" are acquired and occur as a sequel to asthma, chronic bronchitis, chronic pneumonitis and acute respiratory infections. We have found that staphylococcic pneumonia is the commonest cause of radiolucent areas in the lungs during infancy. Other rare conditions such as duplications of the stomach or esophagus must be borne in mind. Emphysema, tuberculous cavities, bronchiectasis and lung abscesses, discussed by Cassels, Fritz and Adams,[13] usually occur beyond the age group under consideration.

When a cystlike cavity is found in the lungs on roentgen examination, it must be determined as certainly as possible whether it is a congenital cyst or a pneumatocele formed after a respiratory infection. Treatment of the former is surgical excision; treatment of the latter is usually conservative. Differentiation may be aided by consideration of the following points:

1. The history is most important. If a child has had proved staphylococcic pneumonia or if there is a history of severe respiratory illness,

9. Head, J. R., and Avery, E. E.: Intracavitary Suction (Monaldi) in the Treatment of Emphysematous Bullae and Blebs, J. Thoracic Surg. **18**:761 (Dec.) 1949.

10. Pierce, C. B.: Cystic Disease of the Lung, Am. J. Roentgenol. **44**:848 (Dec.) 1940.

11. Caffey, J.: Regional Obstructive Pulmonary Emphysema in Infants and Children, Am. J. Dis. Child. **60**:586 (Sept.) 1940.

12. Almklov, J. R., and Hatoff, A.: Pneumatoceles During the Course of Pneumonia in Children, Am. J. Dis. Child. **72**:521 (Nov.) 1946.

13. Cassels, D. E.; Fritz, J. M., and Adams, W. E.: Cystic Disease of the Lung, J. Pediat. **35**:585 (Nov.) 1949.

a radiolucent area in the lungs is most likely an acquired cyst. During infancy congenital cysts are rarely infected.

2. A cystic cavity found before any respiratory illness has occurred makes almost certain a diagnosis of congenital cyst. If perchance a roentgenogram of the chest has been made before any respiratory infection has occurred and was normal, then the appearance of a cyst afterward would be diagnostic of the acquired variety. A sequence of roentgenograms showing an initial consolidation phase of pneumonia followed by the appearance of "air bubbles" and then resolution of the consolidation and formation of a thin-walled cyst in the lung is strongly indicative of the acquired nature of the disease.

3. Congenital cysts usually maintain a rather constant size while pneumatoceles may fluctuate in size rapidly (Caffey).[11]

4. Congenital cysts may show thicker walls roentgenographically than acquired cysts.

5. Infection in the congenital cyst becomes a more frequent occurrence as the child gets older, but it is rare in the pneumatocele.

6. Head and Avery[9] have inserted a thoracoscope into cysts after initially causing adhesions between the pleural surfaces. The appearance of the lining of a congenital cyst is smooth and glistening like epithelium. Black pigment deposits appear only if the bronchial opening is patent. The appearance of the wall of a pneumatocele is different, being composed of compressed alveoli in a web of interlacing black pulmonary tissue. There may be elongated strands of pulmonary tissue stretching across the lumen of the cavity. If there is any doubt, a biopsy of the wall may be made.

SUMMARY AND CONCLUSIONS

1. Six cases of congenital lung cysts are reported. One case was that of a 5 day old infant treated by lobectomy, with recovery.

2. Nine cases of staphylococcic pneumonia are reported in which, at some time during the illness or thereafter, the condition simulated a lung cyst.

3. Differential diagnosis of congenital and acquired postinfectional cysts of the lung in infants may be difficult but is essential.

4. Congenital cysts of the lung should be treated by excision of the involved lung tissue as early as is feasible. Acquired "cysts" should be observed, since a majority disappear spontaneously. If any treatment is required, it may be conservative.

MIDDLE LOBE SYNDROME

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CHRONIC nonspecific pneumonitis with atelectasis occurring in the middle lobe of the right lung has recently been classified as a clinical entity and been called "middle lobe syndrome." Graham, Burford and Mayer [1] and also Paulson and Shaw [2] have called attention to the lesion. These authors feel that the characteristic pattern of this type of suppuration justifies its separation into a clinical entity. They have mentioned that enlargement of peribronchial lymph nodes has been common in their cases. They emphasize the nonspecific nature of the disease.

We have reviewed our cases of chronic suppurative pulmonary disease to see if there was a characteristic group of symptoms, pathologic picture or roentgen shadow common to all the cases of pneumonitis of the middle lobe. We were unable to find a correlated clinical and pathologic entity peculiar to the middle lobe. We did, however, find 26 patients in whom we felt that involvement of hilar lymph nodes was directly responsible for the obstruction that resulted in chronic nonspecific pneumonitis. In this report we shall review these cases and discuss some of the views presented in the literature.

ANALYSIS OF CASES

The report is based on a study of 26 patients. There were only 8 of these patients who fell into the specific category that could be called middle lobe syndrome in that only the middle lobe was involved and the pneumonitis was nonspecific. However, there were 3 additional

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Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

1. Graham, E. A.; Burford, T. H., and Mayer, J. H.: Middle Lobe Syndrome, Postgrad. Med. **4**:29 (July) 1948.

2. Paulson, D. L., and Shaw, R. R.: Chronic Atelectasis and Pneumonitis of the Middle Lobe, J. Thoracic Surg. **18**:747 (Dec.) 1949.

patients with the same clinical, roentgenologic and laboratory findings as the others but for whom a diagnosis of tuberculosis was returned by the pathologist. In another 6 patients the middle lobe was primarily involved with nonspecific pneumonitis, but in addition a segment of either the upper or the lower lobe of the right lung was also involved. In still another group of 9 patients the same lesion was found, but the

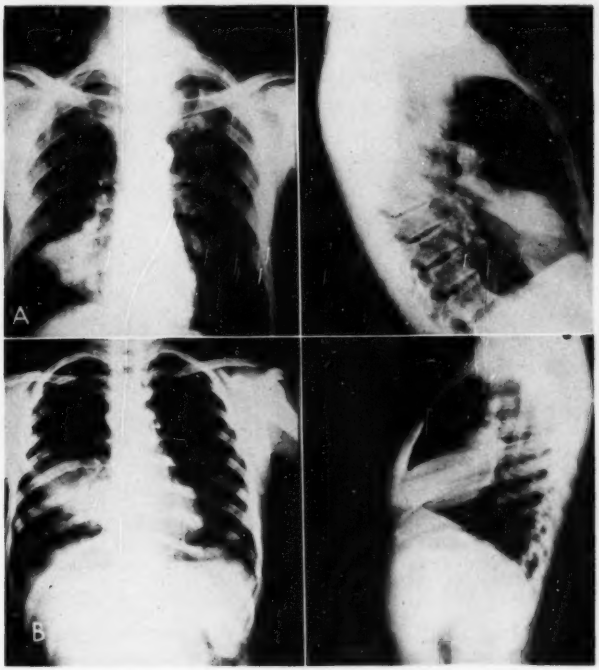

Fig. 1.—Roentgenograms showing, *A*, atelectasis at lateral division of middle lobe and *B*, atelectasis of medial division of middle lobe.

pathologic condition was located in the upper or the lower lobe of the left lung, with the upper lobe more frequently involved.

In all the 8 patients in whom the disease was confined to the middle lobe, calcified lymph nodes in the region of the middle lobe bronchus were demonstrated. This was also true of the patients with nonspecific pneumonitis in segments of other lobes. Three of the 8 patients had negative tuberculin reactions, and 1 had a negative

tuberculin but positive histoplasmin reaction. Two patients gave a history of having coughed up broncholiths. Cough, hemoptysis and pain in the chest were characteristic symptoms in all the patients, hemoptysis being the most outstanding symptom.

ROENTGENOLOGIC STUDY

The roentgen shadow characteristically produced by shrinkage of the middle lobe was commonly interpreted as interlobar effusion prior to 1938, when Hampton and King [3] pointed out that disease of the lateral aspect of the middle lobe may produce a triangular shadow (fig. 1 *A*), whereas disease of the medial aspect may produce a rectangu-

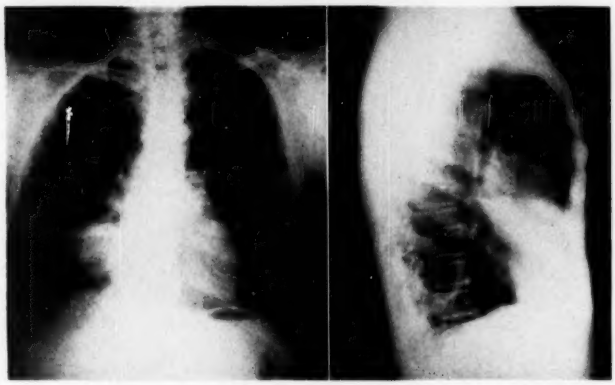

Fig. 2.—Roentgenogram showing atelectasis of middle lobe and also of segment of lower lobe.

lar shadow (fig. 1 *B*). They also showed that interlobar effusions are rare and that the common shadow in the middle lobe which is interpreted as interlobar effusion is attributable to pneumonitis. Pneumonitis may be seen in other parts of the lung because of bronchial obstruction from enlarged lymph nodes (fig. 3). The common roentgenologic finding in all our patients was the demonstrable calcified hilar lymph nodes (fig. 4).

3. Hampton, A. O., and King, D. S.: The Middle Lobe of the Right Lung: Its Roentgen Appearance in Health and Disease, Am. J. Roentgenol. **35**:721 (June) 1936.

PATHOLOGIC PROCESS

Waddell, Sniffen and Sweet [4] described a group of cases of chronic pneumonitis in different lobes of the lung. Their cases were characterized by interstitial pneumonitis and unusual cholesterol deposits. They

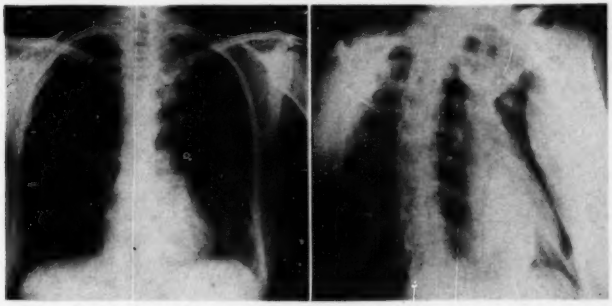

Fig. 3.—Roentgenogram showing atelectasis of segment of upper lobe of left lung with calcified hilar lymph nodes.

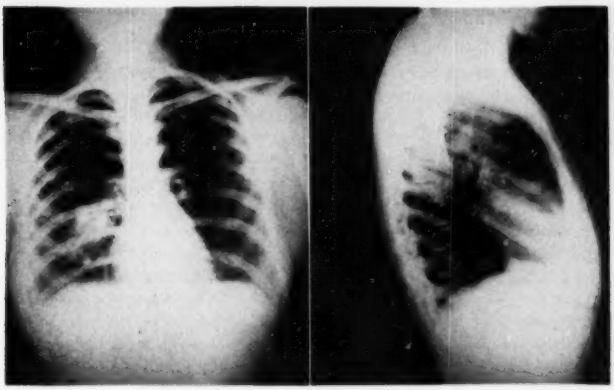

Fig. 4.—Roentgenogram showing atelectasis of middle lobe with calcification of hilar lymph nodes.

mentioned that in the majority of their cases there were large, firm, chronically inflamed hilar lymph nodes.

4. Waddell, W. R.; Sniffen, R. C., and Sweet, R. H.: Chronic Pneumonitis: Its Clinical and Pathologic Importance; Report of 10 Cases Showing Interstitial Pneumonitis and Unusual Cholesterol Deposits, J. Thoracic Surg. **18**:707 (Oct.) 1949.

One of our pathologists, Dr. Eleanor Valentine,[5] was unable to find a pathologic picture characteristic of the middle lobe syndrome. The following descriptions of the microscopic observations illustrate the varying pathologic processes, although the roentgen findings in the 3 cases were identical.

CASE 1.—Multiple sections from the lung tissue show the alveolar pattern to be universally and greatly distorted by the presence of a decided inflammatory lesion. The latter consists essentially of scattered microscopic abscesses, the walls of which are composed of dense infiltrations of chronic inflammatory cells, the majority being plasma cells. Eosinophils are also a prominent feature. The surrounding tissue is the site of a considerable degree of fibrous scarring, aggregations of lymphoid tissue being scattered throughout this area. Many of these show follicle formation. There are occasional areas of relatively normal lung tissue, some of which is edematous, while other portions are atelectatic. An occasional large bronchus is seen which is densely infiltrated by similar inflammatory cells and contains neutrophils. In general, however, bronchiolar elements are sparse. In an occasional area there are numerous macrophages which appear to contain lipid material surrounding the abscesses. The lesion here appears to be largely that of chronic pulmonary suppuration, the origin of which cannot be ascertained from histologic examination.

CASE 2.—Multiple sections from the lung show the alveolar parenchyma to be largely replaced by dense fibrous tissue in which an occasional island of atelectatic lung or regenerating alveoli may be seen. There are also numerous collections of lymphoid tissue, many showing secondary follicle formation. In this lung the bronchi and bronchioles are prominent, and there appears to be proliferation of the latter. The larger bronchi show a marked degree of chronic inflammatory infiltration and fibrous thickening of their walls. The bronchioles are dilated and similarly involved. There are numerous arterioles which are prominent because of thickening of their walls almost to the point of obliteration of their lumens caused by intimal proliferation. The lesion in this instance appears to be largely that of chronic bronchiectasis with pulmonary suppuration and fibrosis.

CASE 3.—Multiple sections from the lung tissue in this case show the normal structure to be largely replaced by a deposit of collagenous fibrous tissue which occurs in solid masses and also isolates the alveoli by thickening their walls. In some areas this tissue has the appearance of being practically necrotic, and there are localized nodules showing calcific deposits in this necrotic-appearing tissue. These circumscribed lesions of necrosis and calcification are highly suggestive of an old, healed tuberculosis. The changes are extensive, replacing to a large extent the alveolar markings in the sections taken. There is only a moderate amount of lymphocytic infiltration in scattered portions of this tissue. Essentially the lesion appears to be much less actively inflammatory than the others and strongly suggestive of a tuberculous process, although this cannot be definitely established.

Reports are numerous of childhood tuberculosis producing atelectasis or pneumonitis of a lobe or a segment of a lobe. Kent[6] noted that

5. Valentine, E. H.: Personal communication to the authors.

6. Kent, E. M.: Bronchial Obstruction and Pulmonary Atelectasis: As Seen in Childhood Tuberculosis with Secondary Bronchiectasis as Sequela, Am. Rev. Tuberc. **46**:524 (Nov.) 1942.

enlargement of peribronchial and hilar lymph nodes was common in children and that such nodes could cause atelectasis from compression of the wall of the bronchus. Court [7] described a collapse of the middle lobe in a child who had a family history of tuberculosis, but no active

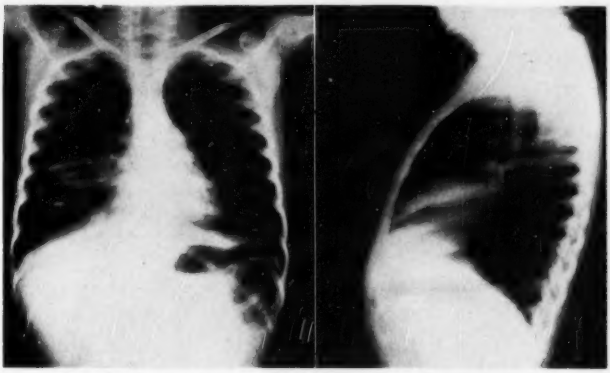

Fig. 5.—Roentgenogram of child with family history of tuberculosis. The atelectatic middle lobe is probably due to tuberculous hilar lymph nodes.

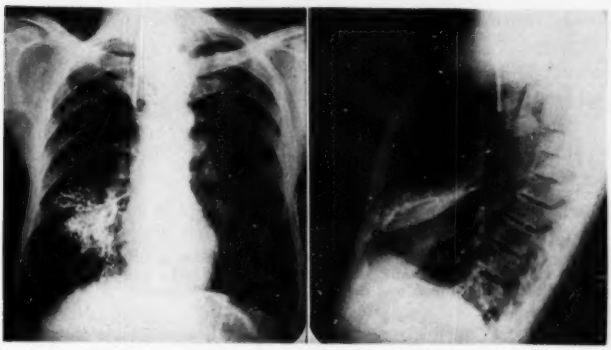

Fig. 6.—Bronchogram of patient with atelectasis of middle lobe showing blockage of medial segment of middle lobe.

tuberculosis could be found. One of our cases (fig. 5) was similar to the case described by Court.

7. Court, S. D.: Right Middle Lobe Collapse, Proc. Roy. Soc. Med. **31**:1156 (Aug.) 1938.

ANATOMIC CONSIDERATIONS

Brock,[8] in a careful study of the anatomy of the lung, brings out the point that in addition to the middle lobe of the right lung the bronchi of the upper and lower lobes of the left lung are also liable to be compressed by the many glands which surround them at their origin. He stresses, however, that the middle lobe bronchus remains

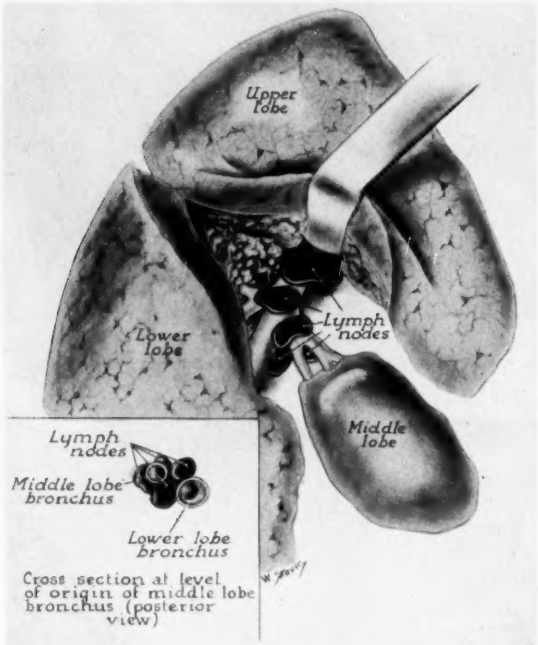

Fig. 7.—Drawing showing distribution of lymph nodes at origin of middle lobe bronchus and atelectatic middle lobe. Cross section shows lymph nodes between middle and lower lobe bronchi at origin of middle lobe bronchus.

the most exposed to this risk. A drawing made at the time of operation on one of our patients illustrates this point (fig. 7).

Brock further explains the obstructive mechanism by reasoning that if a caseous gland adheres to the wall, ulcerates through it and discharges its contents into the lumen of the bronchus, permanent

8. Brock, R. C.: The Anatomy of the Bronchial Tree with Special Reference to the Surgery of Living Abscess, New York & London, Oxford University Press, 1946.

stricture or even complete obliteration follows. He feels that a damaged lobe or segment of a lobe may remain silent for many years and suffer from infection late in the patient's life. The original caseous gland, he points out, which caused the bronchostenosis may have discharged its content into the lumen many years before so that nothing remains of it to calcify, although severe peribronchial fibrosis will have resulted.

PATHOGENESIS

A critical review of our patients would seem to bear out the contentions of Brock. In the first place, the nonspecific pneumonitis and atelectasis which were commoner in the middle lobe were also found in other lobes, particularly the upper lobe of the left lung. The most striking feature in the majority of the cases was the presence of demonstrable calcified lymph nodes in the region of the diseased lobe or segment. Furthermore, evidence of involvement of the bronchial wall was common. In 4 patients this evidence was obtained at bronchoscopy by biopsy, which showed chronic submucosal inflammation with squamous epithelial metaplasia. In 2 other patients broncholiths had been expectorated.

We agree with the other authors that the chronic pneumonitis is a result of obstruction, with resulting infection. The obstruction is brought about by lymph node involvement either from pressure alone or from pressure and stenosis of the bronchial wall.

While most of our patients had no demonstrable tuberculosis either clinically or on examination of the resected lobe and while 4 patients had negative tuberculin reactions, we still believe that tuberculosis contracted and healed years before might well have been responsible for the subsequent bronchial occlusion and resulting pneumonitis. In healed tuberculosis the tuberculin reaction may become negative if reinfection has not taken place.

We agree with Head [9] in his comment on Paulson and Shaw's article. Head stated that he thought the discussion should not be limited to involvement of the middle lobe. We think that more attention should be given to the lymph glands at the hilus in the evaluation of parenchymal disease in the lung.

TREATMENT

The roentgen findings in this type of chronic pneumonitis are indistinguishable from the findings in bronchogenic carcinoma. Also the symptoms are identical in that hemoptysis, cough and pain are prominent features, whether the lesion is malignant or inflammatory. Resection of the lung is the treatment indicated because the inflammatory process

9. Head, J., in discussion on Paulson and Shaw.[2]

is not reversible. Therefore, bronchogenic carcinoma should be ruled out if the diagnosis of carcinoma cannot be made preoperatively. Only the diseased lung tissue should be removed if it is inflammatory disease; if carcinoma is found, more radical surgical procedures should be carried out.

SUMMARY

A study of patients with chronic pneumonitis and obstructive atelectasis of the middle lobe of the right lung did not show characteristic features which were different from those in cases of pneumonitis and collapse in other lobes as a result of bronchial compression from chronically inflamed and calcified lymph nodes. However, the middle lobe was found to be more susceptible because of its anatomic peculiarities.

Chronic inflammation and calcification of the hilar lymph nodes seem to be of significance in the pathogenesis of chronic nonspecific pneumonitis. Removal of the involved segment is the treatment indicated because of the irreversible nature of the suppurative disease, as we have previously emphasized.[10]

10. Harper, F. R.; Condon, W. B., and Wierman, W. H.: Suppurative Disease of the Lungs, Arch. Surg. **58**:819 (June) 1949.

PLEURAL DECORTICATION IN THE PREVENTION AND TREATMENT OF THORACOGENIC SCOLIOSIS

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AND
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THE FORMATION of a dense layer of fibrous tissue in the pleural space always results in some degree of scoliosis. When this condition of fibrothorax originates in adult life, the scoliosis is seldom sufficiently severe to constitute a disability; decortication, when it is done, is to improve respiratory function or to cure chronic empyema. In children the growth of the spine introduces another factor which leads to a progressive deformity, the eventual extent of which depends on the degree of fixation of the chest wall and the amount of growth which takes place before the condition is corrected or adult stature reached.

The extreme degree of thoracogenic scoliosis is seen in persons in whom chronic empyema has developed in infancy. The ribs remain infantile in type, crowded together and sometimes fused to each other; they come to resemble the spokes of a wheel, of which the hub is in the axilla and the rim is represented by the thoracic region of the spine. The bodies of the vertebrae are wedge shaped, there is secondary deformity of the ribs of the opposite side and compensatory curves are developed in the lumbar and cervical areas of the spine. The picture resembles that seen in severe idiopathic scoliosis but with the difference that there is a history of chronic empyema, the whole chest on the concave side is contracted both front and back, the whole thoracic region of the spine is involved in the primary curve and the roentgenogram demonstrates a fibrothorax on the concave side.

Between these two extremes, the slight and unimportant scoliosis resulting from fibrothorax developing in adults and the severe, disabling scoliosis resulting from the same condition developing in infancy, may be seen thoracogenic scoliosis of every grade of severity, depending on the age of onset of the primary pleural infection. Correction of such scoliosis cannot be obtained unless the causative factor is removed. In the less severe cases, with no structural change in the vertebral bodies,

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there will be a satisfactory straightening of the spine after pleural decortication followed by breathing and spinal exercises. In the severe group, with gross secondary changes in the spine, treatment of the chest condition is required, followed by slow correction of the primary curve by means of a turnbuckle jacket and fixation in the corrected position by spinal fusion. The operation on the chest is designed to mobilize the thoracic wall so that it may lengthen during correction of the curve; to accomplish this purpose it may be necessary to resect a number of ribs in addition to removing the layer of fibrous tissue ensheathing the visceral and parietal pleurae.

Such a decortication may be extremely difficult. The layer of fibrous tissue may be a few millimeters or up to 2 or 3 cm. in thickness, and it is intimately fused with the visceral pleura. It is impossible to peel this layer from the lung. It must be removed by sharp dissection, with many small wounds of the lung resulting, which close spontaneously or are closed by suture. The whole layer of fibrous tissue should be removed from visceral and parietal pleurae, including the surface of the diaphragm, and at the end of the operation the lung should inflate to fill the thoracic cavity. The thorax is drained by means of closed drainage, which is supplemented by aspirations to maintain complete expansion of the lung.

The following case reports illustrate the treatment of various degrees of thoracogenic scoliosis by pleural decortication.

CASE 1.—F. B., a girl aged 15 years, was admitted to the Toronto Hospital for tuberculosis on Dec. 9, 1946. Because she was a tuberculosis contact, roentgenogram of the chest was made on September 27, which did not reveal pulmonary tuberculosis. While she was under treatment for an eye condition in the Toronto General Hospital on November 3 acute pleurisy with effusion developed. Culture of the fluid yielded the tubercle bacillus, but at no time was there cough or sputum. The chest was aspirated from time to time, and it was noted that there was increasing difficulty in finding fluid. By Feb. 14, 1947, no fluid could be obtained and a needle was introduced with great difficulty. The chest was contracted and immobile, breath sounds were absent and there was slight thoracic scoliosis. Figure 1 *A* demonstrates the roentgen appearance at this time. A diagnosis of tuberculous fibrothorax was made, and it was decided to attempt a decortication.

On May 20, six months after the onset, an intercostal incision was made in the fifth space, with division of the posterior ends of the fifth and sixth ribs. An exceedingly dense layer of fibrous tissue, 2 cm. in thickness, had been deposited on the parietal pleura, while on the visceral pleura it was 2 to 3 mm. in thickness. The pleural space was represented by a narrow slit containing a few cubic centimeters of yellow fluid, in which the tubercle bacillus was demonstrated on direct smear. With some difficulty a complete decortication of lung, thoracic wall and diaphragm was done, and the lung expanded to fill the space. Recovery was uneventful. Streptomycin was not used.

Figure 1 *B* shows the roentgenologic appearance of the chest eight months later. At this time, complete correction of the beginning scoliosis, normal chest function and normal vital capacity were evidenced. The patient has remained perfectly well.

This case demonstrates the use of decortication relatively early after the onset of fibrothorax, chiefly to recover pulmonary function but also to prevent further scoliosis.

Case 2.—M. G., a youth aged 18 years, was admitted to the Toronto General Hospital on May 18, 1948, complaining of recurrent infection in the right side of

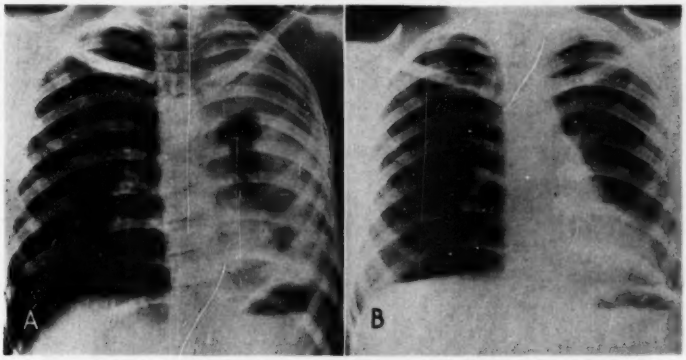

Fig. 1 (case 1).—*A*, preoperative roentgenogram. *B*, eight months after operation.

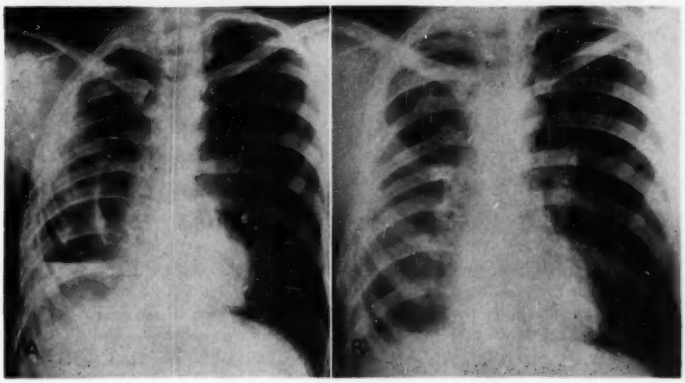

Fig. 2 (case 2).—*A*, preoperative roentgenogram. *B*, seventeen months after operation.

the chest. At the age of 8 postpneumonic empyema developed. The fluid had been drained on five occasions but had persisted, with a bronchopleural fistula. At the time of the patient's admission the thoracic wall was healed and the bronchopleural fistula was closed. The patient was poorly nourished and short of breath on exertion, and he showed a moderate thoracic scoliosis, concave to the right. The right side of the chest was small and contracted, and there were signs of fluid. Thick pus

was aspirated from the right side of the chest, and Staphyloccocus aureus was cultured from it. There was no evidence of tuberculous infection. Figure *2 A* shows the roentgen appearance on the patient's admission. The moderately severe thoracic scoliosis is evident, but there is no wedge deformity of the vertebrae.

On June 8, 1948, the right side of the chest was opened by means of resection of the fifth rib and a complete decortication carried out with moderate difficulty. The lung remained well expanded. Breathing and posture exercises were commenced early, and the patient was discharged eighteen days after operation. When last seen, seventeen months later, he showed marked improvement in general health and exercise tolerance and good air entry into the right side of the chest. Figure *2 B* shows the improvement in the scoliosis.

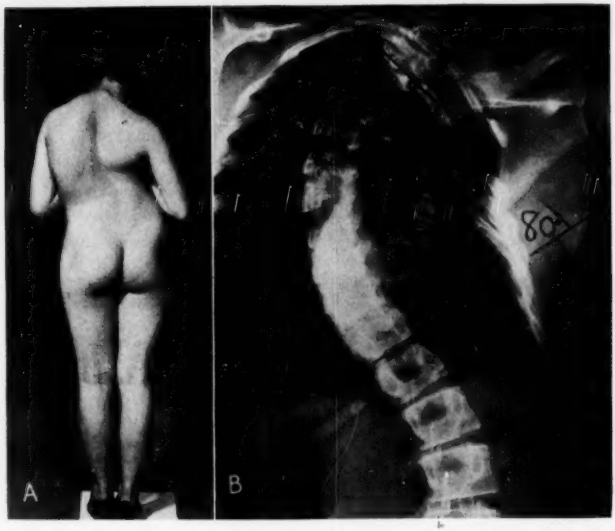

Fig. 3 (case 3).—*A*, patient before operation. *B*, preoperative roentgenogram.

This case illustrates the improvement obtained in a case of moderately severe scoliosis of long standing by simple decortication followed by exercises.

Case 3.—G. McT., a girl aged 14 years, was admitted to the Toronto General Hospital on Oct. 19, 1948, complaining of spinal deformity. At the age of 7 months the patient had pneumonia, and empyema developed on the right side which drained for four years, with discharge of sequestra from the ribs. At the age of 9 years the mother had noticed a deformity of the back which had steadily increased. The patient's general health had remained good. Examination showed a well developed and well nourished girl with severe scoliosis. The primary curve was in the thoracic region, concave to the right and fixed; the right side of the chest was markedly contracted, with evidence of thickened pleura and little function. Figure *3 A* demonstrates the degree of scoliosis. Figure *3 B* is a roentgenogram of the spine and chest demonstrating the curvature of the spine and obvious wedge deformity of the

vertebral bodies. The ribs are crowded together in the right axilla, and the fourth and fifth and eighth and ninth are fused to each other. The fibrothorax is only of moderate thickness.

On Nov. 9, 1948, the right side of the thoracic wall was exposed and the second, sixth, eighth and the ninth ribs were widely resected. To mobilize the bony thorax further the third, fourth, fifth and seventh ribs were fractured by resecting a short segment in the midaxilla. At this point it was noted that the dense pleural membrane, which was 3 mm. in thickness, was stretched taut and was preventing correction of the curve. It was completely resected, with resulting immediate

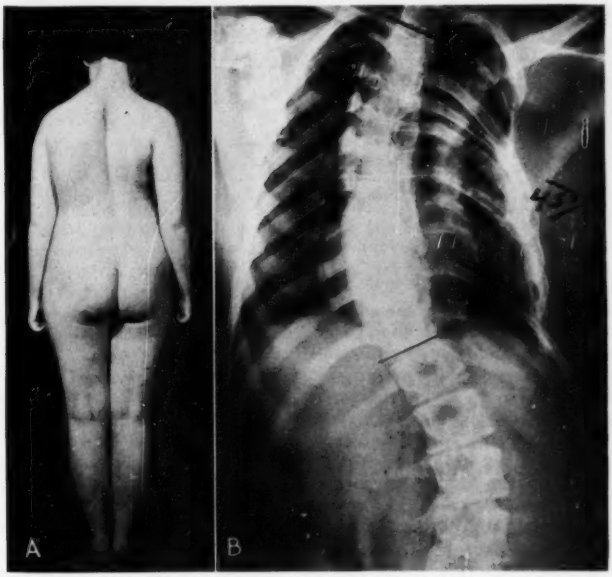

Fig. 4 (case 3).—Photograph (*A*) and roentgenogram (*B*) of patient one year after spinal fusion.

improvement in the primary curve. The patient made a good recovery from this extensive operation, and twelve days later a hinged plaster jacket was applied and further correction of the primary curve commenced. The correction was gradually increased until it was judged satisfactory, and the spine was then fused from the first to the eleventh dorsal vertebra inclusive in two stages, on February 3 and 28. The improvement one year later is shown in figure 4. It may be noted that the primary curve has been reduced by 35 degrees, that the patient is now well balanced, the shoulders level and the head carried erect without difficulty.

This is an example of the most severe type of thoracogenic scoliosis with gross anatomic changes in the spine. Mobilization of the thoracic wall, including pleural decortication, was a necessary preliminary to treatment of the scoliosis.

SUMMARY AND CONCLUSIONS

The use of pleural decortication in the prevention of progressive thoracogenic scoliosis and in the treatment of the established condition has been discussed and illustrated by case reports.

Ideally, the development of fibrothorax should be prevented, except possibly in an occasional case of tuberculous pleuritis, by the proper management of acute empyema. If it has already occurred, the resulting disability in terms of persisting loss of pulmonary function and progressive scoliosis can be corrected by pleural decortication, which in some patients may be supplemented by operative measures directed to the spine. Experience with the cases described here and others indicates that it is possible to carry out a satisfactory decortication many years after the onset of the original pleuritis, although the operation may be difficult.

DISCUSSION

OF PAPERS BY DRS. DORSEY AND SCANLON, POTTS AND RIKER, HARPER AND OTHERS AND KERGIN AND DEWAR

DR. LEON J. LEAHY, Buffalo: I should like to discuss the paper by Dr. Potts and Dr. Riker. First, a problem that is sometimes confusing when these instances are being collected, is the question of when an infant becomes a child. I do not know of any arbitrary age, but I noticed that in the Sunday paper it was set at 2 years for the purpose of basing a tariff on infants' and children's clothes, so maybe that might be a good precedent to follow. It does not apply in this instance, because all our patients are under 1 year.

In reviewing our resections for cystic disease in infants, we found 3 cases in which there was an error in diagnosis. In all these careful bronchoscopic and roentgenologic examinations were carried out, and we fell into the same type of error as Dr. Potts. The first patient was an infant admitted to the Children's Hospital at the age of 11 weeks. Delivery had been difficult, and it had been necessary to institute mechanical resuscitation for a while. There was a wheeze, and the child had acute respiratory episodes with cyanosis; it was necessary to keep it in an oxygen tent. At the age of 14 weeks we removed the upper lobe of the left lung.

(Slide) You will notice that the picture to your left shows a large mediastinal hernia from the left side of the chest into the right side and displacement of the heart—a picture not dissimilar to that which Dr. Riker showed. We thought that this child had a cystic left upper lobe or possibly an entire lung which contained congenital cysts, and we performed lobectomy.

(Slide) This shows the lobe which was removed. It did not collapse on removal and had no apparent cysts. The bronchus was open, as had been determined on bronchoscopy preoperatively. The culture from the bronchus in this instance before operation showed a colon bacillus, and it appeared to be an emphysematous lobe without obstruction of the bronchus.

(Slide) Photomicrographs showed distended alveoli with rupture in some instances and a small amount of exudate but nothing whatever of a cystic nature. We classified this case as hypertrophic emphysema of the upper lobe of the left lung. The child was converted to normal after operation. I do not think that our error (except from a matter of pride) was much of an inconvenience.

The second patient was an 8 month old child, weighing 18½ pounds (8 Kg.), with respiratory infection and cyanosis. Oxygen was necessary. Sulfonamide drugs were administered—I do not know in what amounts—before the child was admitted to the hospital, and there were repeated convulsive attacks which we thought might be on an anoxic basis. The temperature went up to 104 F.

The diagnosis of a cystic lung was made, and the child was operated on, with proposed pneumonectomy.

(Slide) These are the preoperative roentgenograms, showing a somewhat similar condition, with a distended right lung and a mediastinal hernia.

(Slide) At the time of operation we found an organized fibrothorax binding the incarcerated lung down in the gutter. After decortication complete reexpansion took place, and the child was then normal.

The next case is somewhat more detailed. Shortly after birth rapid, labored respirations with cyanosis developed. in an infant. Oxygen was necessary, and the temperature was elevated. Bronchoscopy revealed a right main bronchial occlusion caused by swelling and secretions. The infant made a rather dramatic improvement after bronchoscopy but was readmitted three weeks later with cyanosis, labored respirations and an appearance of pleural effusion. Tapping was done seven or eight times, and 30 to 80 cc. was withdrawn in each instance. This contained chiefly lymphocytes, with a protein content of 0.8 to 0.7. Roentgenograms at this time showed a change, with pocketing fluid levels and air.

(Slide) This is the appearance of the child at the time of the first admission, showing what appears to be the opacity on the left side.

(Slide) This is after tapping, which gives more detail, and is the one which led us to the mistaken diagnosis of cyst, with the translucent areas and fluid levels.

The child was operated on at the age of 5 weeks. A thin-walled cyst was found between the pleura and the endothoracic fascia. This paralleled the esophagus and had a projection which ran down to the cardia of the stomach.

(Slide) This is a gastrogenic cyst. The child likewise made a splendid recovery and was converted to normal.

In another instance we almost made a mistake, but some good fortune deterred us after the child was admitted to the hospital, and we discovered before surgical intervention that cystic fibrosis of the pancreas was present, which I think is another condition that must be borne in mind when one makes a diagnosis of congenital cystic lung.

Dr. William Adams, Chicago: I have enjoyed hearing these papers, which have been both informative and stimulating. I shall confine my remarks chiefly to two of them.

The paper on mediastinal tumors was very interesting. This group of lesions presents problems in both diagnosis and treatment. In my experience, most malignant tumors have not been amenable to surgical therapy. The benign lesions are usually found incidentally on examination or when they have enlarged enough to press on adjacent tissues or structures, interfering with their function.

(Slide) The tumor presented first by Dr. Scanlon suggested a case we saw some time ago and offers considerable difficulty in diagnosis. The patient was a young man who had relatively few symptoms except slight dyspnea on extreme exertion. Actually, a diagnosis before exploration was not definitely made, although the roentgenogram on the right, as you see, is somewhat radiolucent and suggests the possibility of a fatty tumor.

(Slide) This shows the tumor of one side at operation, which was largely fat. It was not until the microscopic sections came through that it was found that it had thymic tissue throughout.

(Slide) This shows a microscopic section of a portion of the tumor.

(Slide) We had to approach it bilaterally in order to remove all the tumor. This tumor had given rise to none of the symptoms of myasthenia gravis.

(Slide) Occasionally we see tumors of the mediastinum which cause pressure on the air passages and give rise to pneumonitis and the symptoms caused thereby. This patient came in with a mild cough; he had complained of a cold, but it had largely subsided. The only clue to the diagnosis was some calcification in the upper part of the chest on that side. It is at about the level of the second interspace anteriorly.

(Slide) On exploration he was found to have a large hemangioma which arose from the mediastinum just above the region of the aorta. It could be mobilized well except at its origin.

(Slide) This slide shows a microscopic section of this tumor. You see the many areas of calcification within the lesion.

We have had three hemangiomas of the mediastinum, one of them producing symptoms which involved the spinal canal, with pressure on the spinal cord, and it was not until it was removed that paralysis of the lower extremities was entirely relieved.

(Slide) The subject of the other paper, cystic disease of the lung, has interested us for some time because of the many different diagnostic lesions that this condition may simulate. Until the last few years surgical treatment has not been sufficient to allow one to make a diagnosis before operation in many cases.

This particular case was seen about ten years ago and presented the features of some of those already described. The lesion is simply a large tension cyst containing only air, with pressure collapsing not only that lung but the opposite one as well.

The patients may present an acute condition that must be relieved immediately if they are to survive; this can be done by simply passing a needle into the cyst, aspirating it and connecting it with a tube under water. The pressure was so great in this case that it forced the plunger out of the syringe.

(Slide) This shows replacement of the needle with a tube, which the child wore for about a year. At the present time, of course, we would go ahead with resection. At the end of that time the baby suddenly died of an unrelated condition.

(Slide) This slide shows the autopsy specimen. You see the characteristic appearance of a trabeculated wall of a cyst occupying only the lower lobe. In other words, the large cyst seen in the roentgenogram was only a part of the lung—the lower lobe.

The type which produce tension cysts are usually found in the first few days of life, at least within the first year or so.

(Slide) This shows another type of symptom complex and brings out the point that all these congenital bronchogenic malformations are not large cysts. As you see on the left, there is pneumonitis. After resection of the lower lobe, the upper lobe expanded and made the chest look normal.

(Slide) This shows a section through the lower lobe, no large cysts are seen but only areas of malformation.

(Slide) This is actually no normal development of this patient's lower lobe. It is comparable to the adenomatous stage of the development of a lung seen at the fifth or sixth month.

CONGENITAL STRICTURE OF THE PORTAL VEIN

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AND
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THE PROBLEM of portal hypertension has received a great deal of attention during the past few years, and its pathologic physiology has been greatly clarified by the studies of Whipple and others.[1] The hypertension within the portal system may be due to either intrahepatic or extrahepatic obstruction. The intrahepatic obstruction is most commonly due to cirrhosis of the liver and is characterized by ascites and esophageal varices, in addition to evidence of hepatic dysfunction. Extrahepatic obstruction is generally associated with the syndrome commonly termed Banti's disease, characterized by splenomegaly, anemia, leukopenia and, usually, esophageal varices. The obstruction in the portal system may be in the portal vein itself or in some portion of the splenic vein.[1c] It is usually possible to determine the site of the obstruction by measuring the differential pressures in the splenic, coronary and portal veins, but the cause of the obstruction is more difficult to establish.[2] The commonest cause is thrombosis or cavernomatous transformation of the portal and/or splenic vein. A less common cause is congenital obliteration of the portal vein, and a localized narrow stricture of the portal vein at the hepatic hilus appears to be the least common.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

From the departments of surgery and pathology of the University of Rochester School of Medicine and Dentistry and the Surgical Service of Strong Memorial Hospital and Rochester Municipal Hospital.

1. (*a*) Whipple, A. O.: The Problem of Portal Hypertension in Relation to the Hepatosplenopathies (E. Starr Judd Lecture), Ann. Surg. **122**:449 (Oct.) 1945. (*b*) Rousselot, L. M.: The Role of Congestion (Portal Hypertension) in So-Called Banti's Syndrome: Clinical and Pathologic Study of 31 Cases with Late Results Following Splenectomy, J. A. M. A. **107**:1788 (Nov. 28) 1936; (*c*) The Late Phase of Congestive Splenomegaly (Banti's Syndrome) With Hematemesis but Without Cirrhosis of the Liver: Further Observations on Etiology of Banti's Syndrome and Effect on Prognosis of Certain Variations in the Portal Venous Pattern, Surgery **8**:34 (July) 1940.

2. Blakemore, A. J., and Lord, J. W., Jr.: The Technic of Using Vitallium Tubes in Establishing Portal-Caval Shunts for Portal Hypertension, Ann. Surg. **122**:476 (Oct.) 1945.

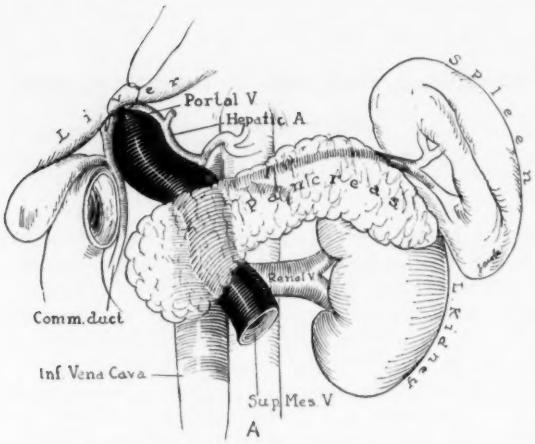

Fig. 1.—Drawing of the stricture of the portal vein found at operation in case 1. Note the dilatation of the vein and the complete occlusion at the site of the stricture.

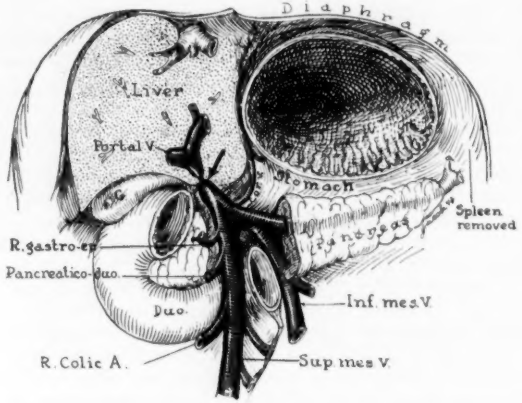

Fig. 2.—Stricture of the portal vein in case 2 (autopsy drawing).

We have had an opportunity to study 2 patients with Banti's syndrome due to stricture of the portal vein, and because both presented such a striking similarity in the clinical and pathologic features, it seems worth while to report on them in detail. Both of the patients with congenital stricture of the portal vein experienced massive hemorrhage from gastric and esophageal varices by the age of 4 years. Splenomegaly was present in each patient and the liver function was normal, with no ascites. The pathologic finding common to both patients was a fibrotic stricture of the portal vein just at the point where the vein entered the liver parenchyma (figs. 1 and *2*). The portal vein proximal to the stricture was markedly dilated, and the portal venous pressure was elevated. One of these patients was examined post mortem, and the intrahepatic portal vein radicles appeared normal. There was complete obstruction of the portal vein by the stricture in both patients.

CASE REPORTS

CASE 1.—R. C., born May 1937, was first admitted to Strong Memorial Hospital on Sept. 1, 1942, with a history that shortly before he had vomited a large amount of bloody material.

Four days prior to his admission, vague, upper abdominal pain had developed and the patient had complained of difficulty in swallowing. On the day prior to his admission he had passed a tarry stool, and four hours before admission he had vomited bright blood, the exact amount being unknown. His past history revealed that he had been admitted to another hospital in the city in November of 1940, where he had complained of cough and weakness and marked anemia had been found. At that time he was 3 years old, but no mention was made of tarry stools. At the age of 4 years he had again been admitted to another hospital because of hematemesis and melena. There was no mention of splenic enlargement, and a diagnosis of questionable purpura had been made. The past history was otherwise noncontributory. The family history revealed that a maternal grandmother had died of leukemia.

On examination, the temperature was 38.5 C. (101.3 F.), the pulse rate 136 and the blood pressure 65 systolic and 0 diastolic. The patient was a poorly nourished but well developed 5 year old boy. He appeared moribund, extremely pale and semiconscious, and the pulse was rapid and thready. The skin showed no evidence of purpura. There were enlarged, tender cervical glands, and the pharynx was injected. The chest was symmetrical; the lungs were clear on percussion and auscultation. The heart beat was rapid, and there was a blowing systolic murmur over the precordium. The superficial veins were prominent over the upper part of the abdomen. The liver was palpable 2 cm. below the costal margin. The spleen was enlarged, and its lower margin extended nearly to the iliac crest. The remainder of the physical examination was noncontributory.

Laboratory Data.—The red blood cell count was 1,010,000; the hemoglobin 3.5 Gm. and the white blood cell count 55,660 (it was later found that the apparent increase in the white blood cell count was due to a large number of nucleated red cells which showed up under the Wright stain and were erroneously designated as myeloid cells). The urine was normal, the nonprotein nitrogen was 34 mg., and the fibrinogen 0.44 Gm. per hundred cubic centimeters. Bleeding and clotting times were normal. Prothrombin time was 23 seconds, with a control of 20 seconds. The platelets numbered 570,000.

Course in the Hospital.—At the time of admission, the patient was in profound shock and was immediately given transfusions of whole blood. During the next ten days he received repeated small whole blood transfusions. He had no further hematemesis, but tarry stools continued for about ten days. By Oct. 19, 1942, the

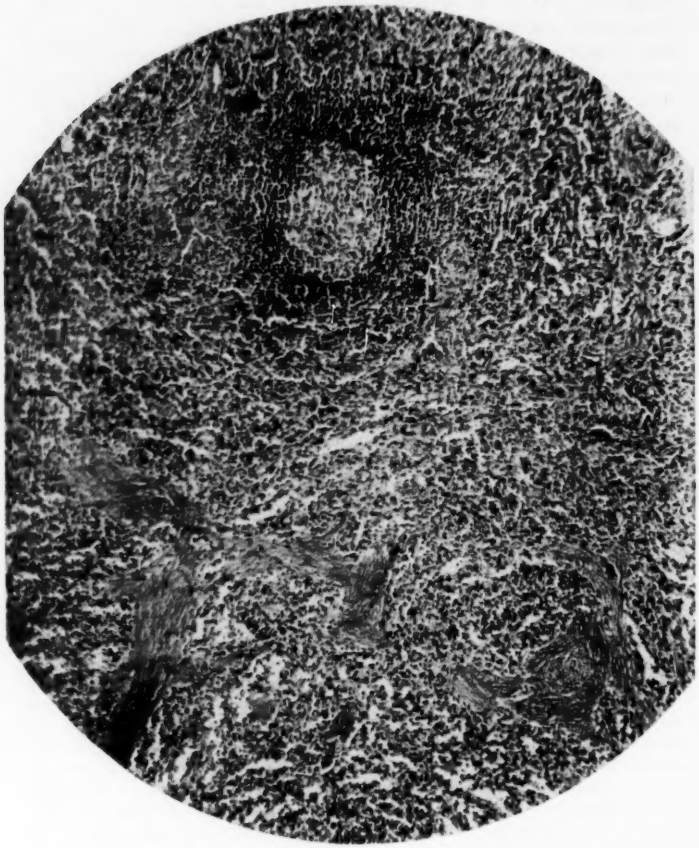

Fig. 3.—Microscopic section of the spleen in case 1.

red blood cell count was 4,040,000, the hemoglobin 12 Gm. and the white blood cell count 5,450. A series of gastrointestinal roentgenograms and one made after barium enema were normal. Because of the enlarged spleen and the apparently abnormal white cell count on admission, the diagnosis of leukemia was considered, but this was not supported by a sternal marrow biopsy. Esophagoscopy was

performed and showed bleeding from the lower third of the esophagus. Bleeding spontaneously ceased, and the patient was discharged on October 25. He was readmitted on November 8 with recurrent hematemesis. In spite of repeated transfusions, his condition was precarious for several weeks, but the bleeding eventually diminished and his condition improved. It was felt at that time that the bleeding was on the basis of esophageal varices which were the result of portal hypertension (Banti's syndrome).

On December 22, exploratory laparotomy and splenectomy were performed. The spleen (fig. 3) weighed 170 Gm. The vasa brevia were markedly dilated, and there were huge vessels at the superior pole of the spleen and around the cardia of the stomach extending to the diaphragmatic hiatus. During manipulation of the spleen, there was profuse bleeding from the mouth, which stopped when these

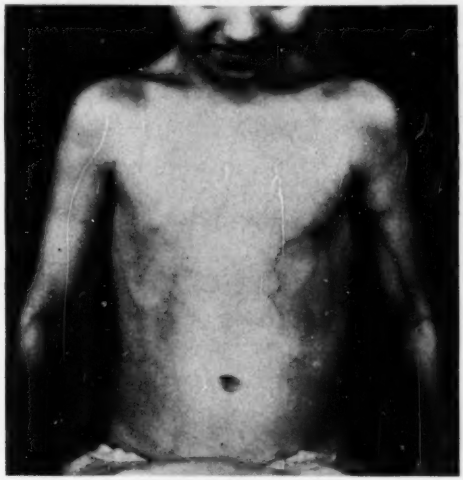

Fig. 4.—Infra-red photograph showing dilated veins in the abdominal wall in case 1.

veins had been tied. Cursory examination of the portal area was made at that time. There was no increased collateral circulation in the hilus of the liver, but the portal vein was not carefully examined.

Postoperative convalescence was uneventful, and there was no evidence of bleeding during the postoperative period. The patient had no further bleeding for a period of one year, but between December 1943 and September 1947 he was admitted to the hospital six times because of major hematemesis, each requiring repeated transfusions. During this time, reexploration of the abdomen was considered in the hope of being able to establish some type of venous shunt between the portal and inferior vena caval circulations. It was felt by various observers that the most probable diagnosis was cavernomatous transformation of the portal vein, and because of this it seemed unlikely that a satisfactory shunt could be performed. There had been no evidence of enlargement of the liver, and ascites had not developed.

Because the bleeding was becoming more severe and more frequent, the patient was finally admitted on Sept. 15, 1947, for operation. At that time, he was 10 years of age and was well developed. The heart still showed a persistent, blowing systolic murmur. Examination of the abdomen revealed a well healed left upper quadrant scar. There was more pronounced dilatation of the veins over the upper part of the abdomen and the lower region of the chest than when he was first seen (fig. 4).

The red blood cell count was 3,600,000; the hemoglobin, 11 Gm. and the white blood cell count 12,000, with a normal differential count. The urine was normal. The icteric index was 10 and the total protein 7.9 Gm., with albumin 5.01 and globulin 2.9 Gm. There was a trace of cephalin flocculation, and thymol turbidity was normal. There was no retention of sulfobromophthalein. The nonprotein nitrogen was 33 mg. and the cholesterol 190 mg. per hundred cubic centimeters.

Operation was performed on Oct. 14, 1947. A transverse upper abdominal incision was made. Exploration revealed no increase in the collateral circulation

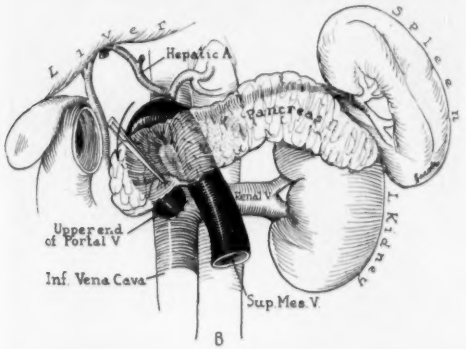

Fig. 5.—End to side anastomosis between portal vein and vena cava in case 1.

in the portal area. The portal vein was identified and found to be tremendously dilated and to have a pressure of over 400 mm. of water. It was dissected out to the hilus of the liver. At the point where the vein entered the liver substance, a complete stricture of the vein was encountered (fig. 1). At this point, there was considerable stenosis of the vein, with practically no lumen. Rubber-shod clamps were placed on the proximal portion of the vein, and it was ligated at the point of the stricture and divided. The vena cava was then mobilized and was temporarily occluded with rubber-shod clamps, and an end to side anastomosis was performed with the use of the vitallium tube method described by Blakemore (fig. 5). When the clamps were removed, the anastomosis appeared to be functioning well and the pressure was 100 mm. of water. During the course of the dissection, a small rent was made in the cystic duct, but this was repaired. The patient tolerated the procedure well. His postoperative course was complicated by a subhepatic collection of bile, which was drained after local anesthesia had been induced. After this there was a small biliary fistula, which eventually closed spontaneously.

Since operation, the patient has been admitted to the hospital twice. The first time was in February 1949 because of a small amount of hematemesis; the bleeding subsided spontaneously. During this stay in the hospital thrombophlebitis of the right leg developed, with rather notable edema, which responded to conservative treatment. He was last seen in December 1949 because of a gastrointestinal upset, and he had had no further bleeding. The esophageal varices can still be seen on roentgenologic and esophagoscopic examination. There are large,

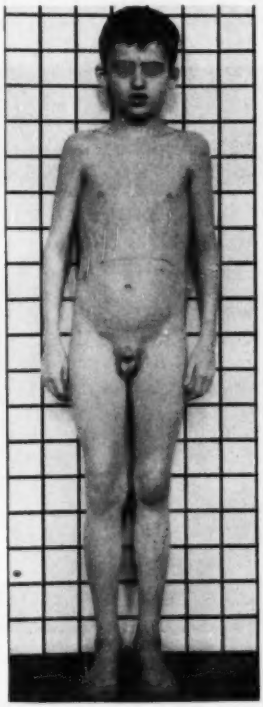

Fig. 6.—Recent photograph showing persistence of dilated veins in abdominal wall in the patient in case 1.

dilated, superficial veins over the upper part of the abdomen and the lower part of the chest (fig. 6). Liver function tests show no abnormality.

Case 2.—The patient was a 4 year old girl who was first admitted to the hospital on Dec. 5, 1947, complaining of intestinal grip. She had been well until five days before her admission, when she first began to feel poorly, complained of abdominal pain and vomited material which was streaked with bright red blood. She continued to be lethargic and on the following day passed a large tarry stool. From then until her admission she had abdominal pain and repeated tarry stools

but no further hematemesis. Her mother noticed that she had become extremely pale and was having a low grade fever. Her past history was essentially noncontributory. She had never had a previous similar episode. The family history was also noncontributory.

When admitted, the patient was acutely ill, appeared pale and was irritable. The temperature was 38 C. (100.4 F.), the pulse rate 160, the respiratory rate 24 and the blood pressure 100 systolic and 80 diastolic. The skin revealed no petechiae or ecchymosis. Examination of the head, ears, eyes, nose and mouth revealed no abnormalities except the pallor of the mucous membranes. There were small, nontender cervical lymph nodes bilaterally. The chest was symmetric,

Fig. 7 (case 2).—Infra-red photograph showing dilated veins.

and the lungs were clear on percussion and auscultation. The heart was normal except for a soft systolic murmur. There were rather prominent superficial veins over the epigastrium and the lower part of the chest (fig. 7). The liver and spleen were both readily palpable 2 fingerbreadths below the costal margin. There was rather vague tenderness in the upper region of the abdomen but no muscle spasm. Rectal and neurologic examinations were noncontributory.

The red blood cell count was 1,910,000, the hemoglobin 3.5 Gm. and the white blood cell count 15,000. The differential count was normal, and the platelets were adequate. The urine was normal, and there was a negative Wassermann reaction. The stools were tarry, with a guaiac reaction of 4 plus. Nonprotein nitrogen was 30 mg. per hundred cubic centimeters, bleeding and clotting time were normal and the hematocrit value was 13 per cent.

The patient received repeated small transfusions after her admission, and on the following day the hematocrit value was rising and the bleeding seemed to be decreased. On the next day she passed several large tarry stools, and in spite of transfusions the hematocrit value continued to fall. Two days after her admission exploratory laparotomy was carried out in an attempt to find a bleeding point in the gastrointestinal tract. With the patient under ether anesthesia, a right rectus incision was made. Blood was found throughout the entire tract from the stomach to the rectum. There was some edema of the gastrohepatic ligament and of the peritoneum in the region of the hepatic hilus, but no bleeding point was found. There was no evidence of increased collateral circulation about the hilus of the liver. The patient tolerated this procedure rather poorly, and the bleeding point was not found. Postoperatively she continued to pass tarry stools and had several episodes of hematemesis. Seven days after the first exploration it was felt that her situation was precarious because of continued hemorrhage. Esophagoscopy was performed, but no bleeding varices were found in the esophagus. On December 15 the abdomen was reexplored with the patient under ether anesthesia. The stomach was widely opened, and a bleeding point from a large vein along the lesser curvature of the stomach was found. This was ligated without difficulty, and the opening in the stomach was closed with two layers of interrupted silk. Venous pressure readings were then performed in the coronary system and found to be over 400 mm. of water. It was felt that the bleeding was the result of portal hypertension, with varices in the cardia of the stomach. It was not felt that her condition would warrant any type of a shunt operation.

After this procedure, the patient had intermittent bleeding, but at no time was there a major hemorrhage, and by Feb. 1, 1948, her hemoglobin content was 12 Gm. and her red blood cell count 4,000,000. The postoperative convalescence was complicated by infectious mononucleosis, and she was discharged to return later for a further operative procedure. She did not return to the hospital as soon as had been anticipated, and on May 8, 1948, five months after the original episode, she was admitted to the emergency department because of vomiting. For twenty-four hours prior to her admission she had vomited all ingested food and liquids and had complained of crampy abdominal pain.

At the time of her admission the temperature was 37.8 C. (100 F.), the pulse rate 120 and the respiratory rate 20. She appeared moderately ill and in acute pain. There was a well healed right rectus scar in the abdomen. There was moderate distention, and dilated bowel loops were visible. The spleen was much larger than it had been on the previous admission. Roentgenograms of the abdomen showed dilated loops of small bowel. It was felt that the patient had obstruction of the small bowel, probably due to adhesions, and an attempt was made to treat it conservatively by intestinal intubation and by parenteral administration of fluids. The hemoglobin content was 12.8 Gm., the red blood cell count 4,300,000 and the white blood cell count 10,700. The urine was normal. Shortly after her admission, she vomited bright red blood, and the Levin tube drainage continued to be bloody. The following day the abdomen was more distended, and the temperature was 39.7 C. (103 F.). Operation was performed with the patient under ether anesthesia. The obstruction was found to be due to adhesions binding a loop of small bowel to the anterior parietal peritoneum. These adhesions were released, and the wound was closed. The postoperative convalescence was rather stormy, and she continued to have guaiac-positive stools from May 9 to May 18. From May 18 until June 24 there was no further evidence of bleeding, and her clinical condition

seemed to warrant further operative procedures. On June 24 exploration was performed by one of us (E. B. M.) with the intention of establishing a shunt between the portal and vena caval system. A left thoracoabdominal incision was made after intratracheal ether anesthesia had been induced. The spleen was

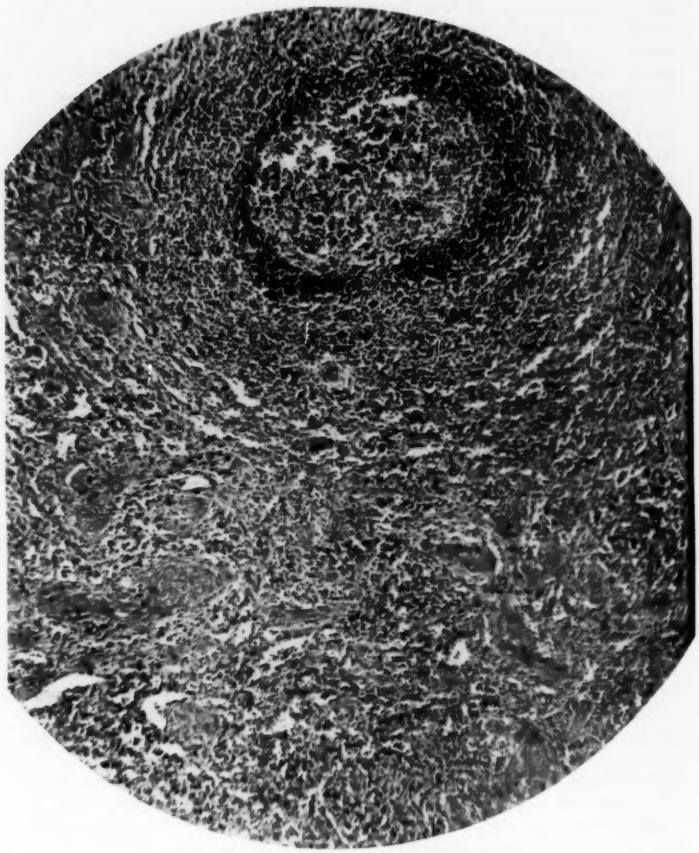

Fig. 8 (case 2).—Microscopic section of spleen.

markedly enlarged. There were large dilated veins around the superior pole of the spleen and in the region of the esophageal hiatus. Pressure in these veins was greater than 400 mm. of water. The spleen was freed without difficulty, and the large venous attachments were ligated. The spleen was removed and the splenic vein dissected until it had been freed up nearly to the head of the pan-

creas, in preparation for a splenorenal anastomosis. The posterior peritoneum was then incised, and the left kidney was mobilized. The renal vein was dissected free, and everything was ready for the performance of end to side splenorenal anastomosis. Until this time there had been little loss of blood and continuous

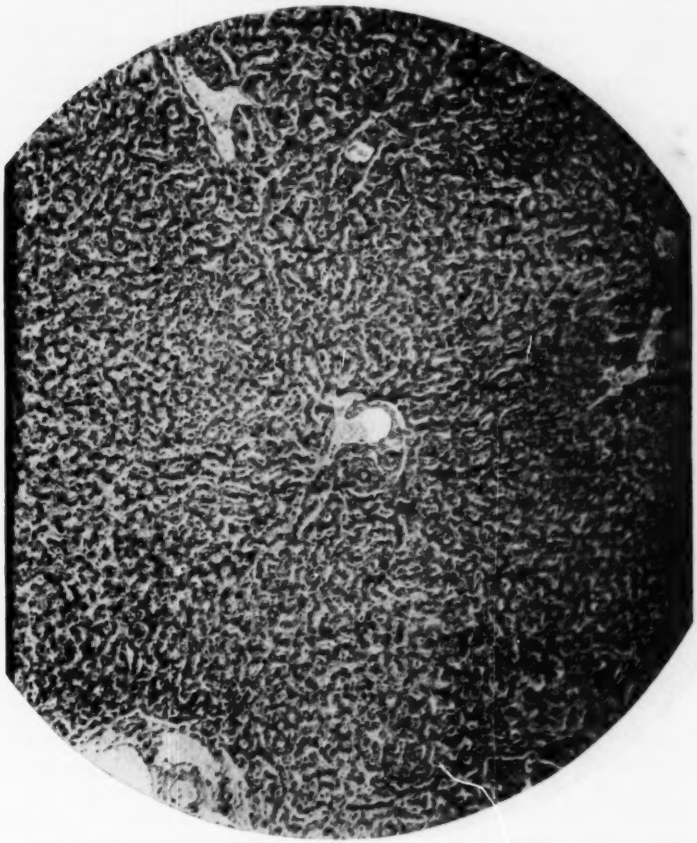

Fig. 9 (case 2).—Microscopic section of liver showing normal architecture.

blood replacement. The patient's condition had seemed good. Her blood pressure suddenly fell just after the kidney was mobilized, and the cardiac action ceased. The heart began beating again after cardiac massage and administration of epinephrine hydrochloride, but the blood pressure remained low and in spite of all resuscitative measures the patient died within a few minutes. The exact cause

of death was not known, and the only difficulty throughout the procedure had been inability to keep the left lung well expanded. Bronchoscopy was performed, but no obstruction to the tracheal-bronchial tree was found. Permission for autopsy was obtained.

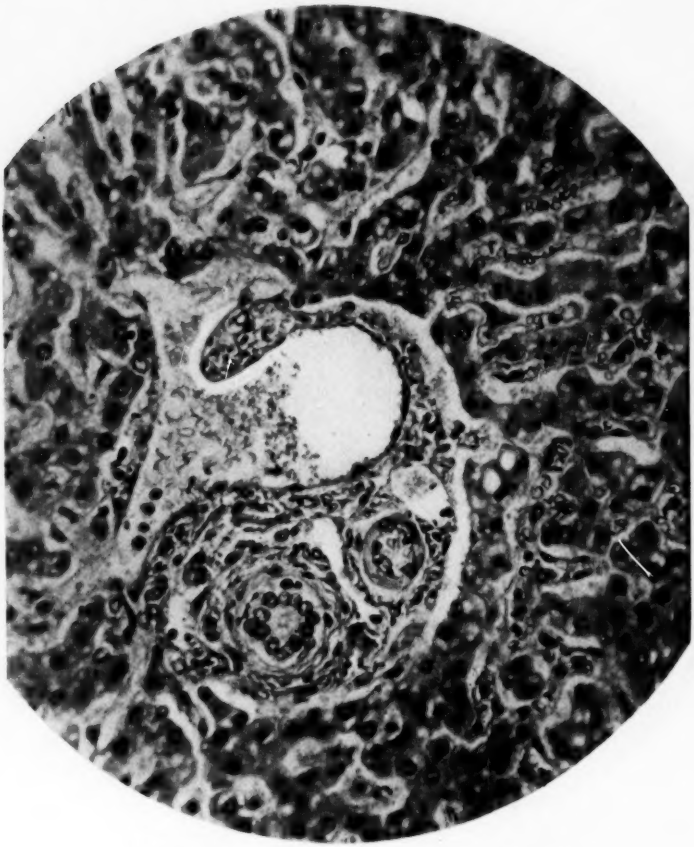

Fig. 10.—Higher magnification of section in figure 9.

Autopsy Report (by L. H.).—The body was that of a white girl 4 years of age. The skin was white and prominent, and large veins were seen in the cervical area, on the superior surface of the extremities and on the anterior surface of the thoracic and epigastric areas. An old 17.0 cm. right rectus incision was present and a recent 17.0 cm. thoracoabdominal incision. Profuse bleeding occurred from the thoracic region of the incision.

The peritoneal cavity contained 200 cc. of sanguineous fluid, and all surfaces were smooth and glistening. Dense adhesions were present between the inferior surface of the left hepatic lobe and the entire lesser gastric curvature involving the gallbladder, duodenum, jejunum and right side of the colon. The spleen was surgically absent, and the ligated splenic vessels were seen.

The left pleural cavity contained 25 cc. of serosanguineous fluid and a collapsed and retracted lung. The pleural surfaces were smooth and glistening. The right pleural cavity contained no fluid. The upper anterior half of the middle and lower lobes were collapsed and retracted about the pulmonary root. The left lung weighed 110 Gm. and the right lung 120 Gm. The lobes of the left lung were red-purple and smooth, and the lung was heavy, firm and noncrepitant. The hilar vessels and bronchi were normal. The bronchioles contained a small amount of yellow mucus. The alveoli were not distinct. The anterior half of the right middle lobe was not remarkable grossly and on cut section, and the bronchioles contained mucus. The esophagus had a normal wall, and large varices were seen in the subserosa and submucosa in the distal two thirds. These united with the branches of the dilated gastroesophageal branches of the dilated coronary vein.

The liver weighed 470 Gm., had a smooth capsule and was red-brown. Adhesions were as described. The cut section was not remarkable.

The Vascular System: The general arterial system was not remarkable except for the hepatic artery, which was enlarged about one and one-half times. The portal system was dilated. The coronary, gastroepiploic, superior mesenteric and right colic and splenic veins were markedly dilated. The portal vein proper at the point of entrance into the hepatic hilus was occluded by a complete fibrotic congenital stricture. The area was strictured down to a 1 mm. fibrous cord. Three millimeters distal to the stricture a small, transverse, fibrous septum was seen, totally occluding the vein lumen. Distal to the obstruction the portal vein measured 8.0 mm. Examination of the intrahepatic portal radicles revealed normal architecture.

The pertinent microscopic changes were limited to the liver, spleen, lungs and esophagus.

Liver: Sections show normal epithelial cords and congested sinusoids. Occasional areas of periductal fibroses and "round cell" foci are seen.

Spleen: A normal capsule is present. The trabeculae are thickened in areas, and the sinusoids are dilated. Fibrosis is evident throughout.

Esophagus: Numerous, large, dilated, submucosal veins were seen throughout the sections.

COMMENT

The difficulty in the management of this problem is illustrated by the 2 cases reported. The patients are first seen with acute gastrointestinal bleeding, and valuable time is lost in attempting to establish the diagnosis and in finding the source of the hemorrhage. The first patient's condition had been diagnosed as purpura at another hospital, and on his admission here it was thought to be leukemia. When this diagnosis had been ruled out, the finding on esophagoscopic examination of bleeding from the lower third of the esophagus helped in establishing the probability of congestive splenomegaly. At that time (1942) the rationale of the portal-caval operations had not yet been established, and only a splenectomy was performed. As is now well known, this procedure does temporarily reduce the tendency to bleed by reducing the

volume of portal blood flow, but hemorrhages recur. There was then a long delay before a venous shunt was attempted. In this situation, an end to side portacaval anastomosis is ideal, but at the present time we would prefer to do a direct suture of the vessels rather than a vitallium tube anastomosis.[3]

In the case of the second patient, the diagnosis should have been made at the first exploratory operation by means of differential venous pressures. The two early operations undoubtedly contributed to the acute bowel obstruction, necessitating a third procedure. The cause of the fatality was not determined, but surely the patient was not in good condition at the time the splenorenal anastomosis was attempted, having had three major operations in a relatively short time.

The commonest causes of portal hypertension have been summarized and discussed by Whipple,[1a] Blakemore [4] and Linton and others.[5] These include the following:

I. Intrahepatic
   A. Portal cirrhosis
   B. Thrombosis of hepatic veins (Chiari's syndrome)
II. Extrahepatic (Banti's syndrome)
   A. Congenital
      1. Cavernomatous transformation of portal vein
      2. Congenital obliteration of portal vein
   B. Acquired thrombosis of portal vein or its tributaries
      1. Trauma
      2. Infection
      3. Idiopathic or spontaneous origin.

Only the congenital type of portal vein obstruction is being considered in this report.

Cavernomatous transformation of the vein may be on a congenital basis; the vein does not develop as a single large vessel but is made up of many small tributaries. The total capacity of these many veins is not adequate to accommodate the portal blood flow and hypertension gradually develops. This condition is thought by some (Klemperer [6]) to be

3. Blakemore, A. H.: The Portacaval Shunt in the Surgical Treatment of Portal Hypertension, Ann. Surg. **128**:825 (Oct.) 1948.

4. Blakemore, A. H.: Indications for Portacaval Anastomosis: Analysis of Cases, Surg., Gynec. & Obst. **84**:645 (April [no. 4 *A*]) 1947.

5. Linton, R. R.; Hardy, I. B., Jr., and Volwiler, W.: Portacaval Shunts in the Treatment of Portal Hypertension: Analysis of 15 Cases with Special Reference to Suture Type of End-to-Side Splenorenal Anastomosis with Splenectomy and Preservation of Kidney, Surg., Gynec. & Obst. **87**:129 (Aug.) 1948.

6. Klemperer, P.: Cavernomatous Transformation of the Portal Vein: Its Relation to Banti's Disease, Arch. Path. **6**:353 (Sept.) 1928.

due occasionally to an actual angioma of the portal vein. Probably the commonest cause is the formation of collateral branches following thrombosis of the vein which eventually appear as multiple small branches. The onset of hemorrhage or other symptoms of Banti's syndrome usually occurs in an older age group if the hypertension is due to cavernomatous transformation while symptoms develop at an early age when it is due to congenital obliteration of the vein. The average age at the onset of symptoms in a series of cases collected by Gruber [7] was 21 years. Klemperer reported 23 cases with an age distribution as follows:

10-20 years	1	40-50	7
20-30	4	50-60	5
30-40	5	60-70	1

The age of 2 patients reported on by Rousselot [1c] was not recorded. Linton [8] has reported cavernomatous transformation in a girl of 19 years. It is probable that in younger persons the condition is congenital but in the older group it is more commonly acquired as collateral circulation after thrombosis of the portal vein.

Congenital atresia of the portal vein causes such complete obstruction to the blood flow that gastric and esophageal varices develop early in life and hemorrhage occurs as the first warning of the condition in infancy or early childhood. The 2 patients being described had major hemorrhage at the age of 4, and the boy had episodes of weakness suggesting bleeding at the age of 3 years. The patient in case 4 of Rousselot's series [1c] had the first hemorrhage at 5 years and was found at autopsy to have a stricture of the portal vein similar to that in our cases. Linton [8] has reported on a patient who first bled at the age of 5 years and Blakemore [9] on 2 patients whose first symptoms were at 3 and 5 years. Haaker Fort [10] reported on a patient who was found to have an enlarged spleen at 1 month of age, marked anemia at 6 months and hemorrhage from esophageal varices at 3 years. The exact type of congenital obliteration of the vein is not known in these cases as the portal area was not dissected at operation.

The etiology of congenital atresia of the portal vein is probably related to the changes in circulation which occur at birth. In the fetus,

7. Gruber, G. B.: Beiträge zur. Pathologie der dauernden Pfortaderverstopfung, Deutsches Arch. f. klin. Med. **122**:319, 1917.

8. Linton, R. R.: Porta-Caval Shunts in the Treatment of Portal Hypertension: With Special Reference to Patients Previously Operated Upon, New England J. Med. **238**:723 (May) 1948.

9. Blakemore, A. H.: The Operation of Portacaval Anastomosis: Indications; Report of Cases, New York State J. Med. **47**:479 (March 1) 1947; footnote 4.

10. Haaker Fort, J.: Bloqueo obstructivo congénito de la porta, Rev. san. de policia **5**:115 (May-June) 1945; Gac. méd. **1**:149 (May) 1945.

the vitelline veins, the left umbilical vein and the portal vein unite at the point where the ductus venosus (arantii) originates to shunt placental blood around the liver to the inferior vena cava.[11] Immediately after birth the umbilical vein collapses and the ductus venosus begins to close. The ligamentum teres and the ligamentum venosum are formed by the process of fibrotic obliteration. This obliterative process may involve the entire portal vein, causing complete obliteration, or it may affect only a small segment, resulting in a short, fibrotic stricture at the hilus of the liver (fig. 11).

The amount of collateral circulation which develops about the hilus of the liver and in the gastrohepatic ligament seems to vary considerably,

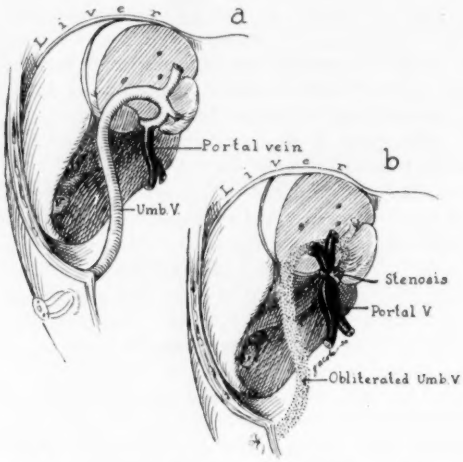

Fig. 11.—Artist's conception of the manner in which a stricture of the portal vein could result in the process of closure of the ductus venosus.

depending on the type of portal obstruction. Anyone who has attempted an anastomosis of the portal vein to the vena cava in a patient with cirrhosis is familiar with the tremendous collateral circulation present. There is also extensive collateral circulation in association with cavernomatous transformation of the portal vein and in complete obliteration of the vein. A striking feature in both of the patients having localized strictures was the lack of vascularity of the portal area. In each instance the portal vein was markedly dilated but it was relatively easy to dissect it free. No troublesome bleeding was encountered from small, fragile

11. Keith, A.: Human Embryology and Morphology, ed. 4, Glasgow, University Press, 1923.

vessels as one sees in cirrhosis. In each patient the hepatic artery appeared dilated and hypertrophied and was probably the main source of blood supply to the liver, whose appearance and function were normal.

These infants or young children are usually first seen by the pediatrician as presenting a problem in the differential diagnosis of hemorrhage in the gastrointestinal tract. If there has been hematemesis of fresh blood, the problem can be narrowed to the sources of bleeding from the esophagus, stomach and duodenum, but if there has been no hematemesis and only tarry stools, the entire intestinal tract must be considered. The most difficult condition to differentiate is a bleeding duodenal ulcer, which is not rare in young children [12] and which may result in exsanguinating hemorrhage. The enlarged spleen often leads to a suspicion of some blood dyscrasia as the underlying cause, but careful examination of the peripheral blood should rule out leukemia and purpura. A bleeding Meckel's diverticulum, a polyp of the colon or multiple hemangiomas of the small intestine must at times be considered. Probably the most important factor in making the diagnosis is to be aware of and thinking about this rare condition. The complete absence of symptoms, the splenomegaly and usually some dilatation of the veins of the abdominal wall should give a clue to the diagnosis. The usual blood picture of Banti's syndrome is obscured by the recent hemorrhage and usually by recent transfusions. Esophagoscopy was a helpful diagnostic aid in the first patient but not in the second, as the varices were mainly in the cardia of the stomach. A barium swallow might yield valuable information and, if performed carefully, is not contraindicated.

The patients should be treated conservatively at first, with whole blood replacement and with careful observation of the hematocrit value and, if possible, the blood volume. In some instances the hemorrhage will cease spontaneously and the patient may be carefully studied. Continued massive bleeding may demand an exploratory operation to find the source of hemorrhage, as in the second case. If no source of bleeding, such as a duodenal ulcer, is found, careful differential venous pressure studies of the coronary vein and the mesenteric veins should be performed. These vessels have not yet become grossly dilated in young children, and inspection is not sufficient for diagnosis. If portal hypertension is found (about 400 mm. of water), the immediate problem is difficult, but it may be necessary to open the cardiac end of the stomach and search for the bleeding point. If none is found, the veins about the esophageal hiatus may be ligated. Ideally, a portal-caval anastomosis

12. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941.

should be done at this time, but the patient is usually not in condition for a prolonged procedure and the surgeon is not psychologically prepared for this eventuality.

If the diagnosis is made without operation, or if there is bleeding postoperatively, balloon tamponage as described by Patton and Johnston [13] and by Blakemore [14] should be tried. In older, cooperative patients this is successful, but it may be difficult to manage in young children.

The only permanent hope of cure is an adequate venous anastomosis between the portal and caval systems. The short complete stricture of the portal vein which was encountered in these 2 patients lends itself admirably to an end to side portal-caval anastomosis. The portal vein should always be carefully explored when a shunt is being contemplated

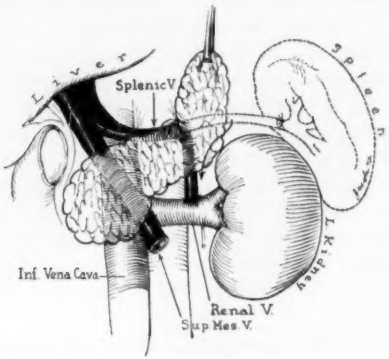

Fig. 12.—Diagrammatic sketch of the splenorenal anastomosis.

in children. The initial exploration may be through a transverse upper abdominal incision; if there is complete obliteration of the portal vein, the incision may be extended and converted to a thoracoabdominal exposure for a splenorenal anastomosis (fig. 12). If a short stricture is encountered with sufficient dilated portal vein to reach the vena cava, the incision can be extended through the right costal margin and the divided end of the portal vein anastomosed to the side of the vena cava (fig. 5). The splenic vein in the second case was large for the size of the patient, but it was much smaller than the portal vein and probably would not have carried all the portal blood. In the first case the portal

13. Patton, T. B., and Johnston, C. G.: A Method for Control of Bleeding from Esophageal Varices, Arch. Surg. **59**:502 (Sept.) 1949.

14. Blakemore, A. H.: Read at a meeting of the Southern Surgical Association, Oct. 1949.

vein was 2 cm. in diameter, and, as has been pointed out by Blakemore,[3] the shunt from portal vein to vena cava will carry a larger volume of blood than the splenorenal anastomosis. If a successful portal-caval anastomosis has been performed, the spleen should probably be removed at a later date if any evidence of hypersplenism exists. If necessary, a splenorenal anastomosis could be done at the time of the splenectomy.

CONCLUSIONS

1. Portal hypertension due to a short congenital stricture of the portal vein results in hemorrhage from gastric and esophageal varices during infancy or early childhood.

2. This pathologic condition must be considered in the differential diagnosis of massive gastrointestinal hemorrhage occurring in very young persons.

3. The most promising method of treatment appears to be a direct anastomosis between the portal vein and the vena cava, since there is complete occlusion of the portal vein.

ARTERIAL HOMOGRAFTS

II. Resection of Thoracic Aortic Aneurysm Using a Stored Human Arterial Transplant

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CLARENCE MAASKE, Ph.D.
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AND
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DENVER

THE PROBLEM of bridging a large gap in a major artery has long been one of importance to both the civilian and the military surgeon. Peirce and his co-workers [1] have recently reintroduced interest in the use of stored arterial homografts for this purpose. In their preliminary studies on dogs these workers demonstrated that such homografts, if taken aseptically within the first few hours after death of the donor animal, could be stored in a standard refrigerator when placed in buffered salt solution containing 10 per cent dog serum. When transplanted into a recipient animal after storage up to fifty days, these homografts would function successfully as a conduit of blood for periods longer than a year. A high percentage of successful "takes" could be obtained by careful anastomotic technics. In addition, it was shown by tissue culture methods that "viable" cells persisted in the stored vessels up to forty days. Gross [2] has subsequently used the stored human arterial homograft in the repair of coarctation of the aorta.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

This study was supported in part by United States Public Health Service grant H-241 and in part by the Life Insurance Medical Research Fund.

From the departments of surgery and physiology, and the Cardiovascular-Pulmonary Research Laboratory, University of Colorado School of Medicine.

1. Peirce, E. C., II; Gross, R. E.; Bill, A. H., Jr., and Merrill, K., Jr.: Tissue-Culture Evaluation of the Viability of Blood Vessels Stored by Refrigeration, Ann. Surg. **129**:333 (March) 1949. Gross, R. E.; Bill, A. H., Jr., and Peirce, E. C., II: Methods for Preservation and Transplantation of Arterial Grafts: Observations on Arterial Grafts in Dogs; Report of Transplantation of Preserved Arterial Grafts in 9 Human Cases, Surg., Gynec. & Obst. **88**:689 (June) 1949.

2. Gross, R. E.: Blood Vessel Grafts, read before a meeting of the Surgery Study Section, National Institutes of Health, United States Public Health Service (Jan. 21) 1950.

In a previous communication,[3] we reported experimental data suggesting that the storage solution can be extremely simple, consisting solely of Ringer's solution to which has been added 10 per cent by volume of homogenous plasma. Vessels stored in this solution in a common refrigerator for as long as six months have been transplanted into recipient animals with consistent success and have remained functional for periods exceeding one year. Careful pathologic study indicated that in the case of short storage grafts, i. e., grafts stored less than forty days, there was often some survival of smooth muscle. In both short storage and long storage grafts the elastic tissue of the media survived relatively intact for many months. All other tissue layers disappeared and were replaced by layers which grew in from the host. It was our feeling that the longer the storage the earlier and more prominent was the appearance of mild degenerative changes in the new vessel. These changes consist of fibrillary destruction of elastic tissue and diffuse calcification of the media and the new intima. In general, therefore, it would appear that grafts stored for less than forty days are preferable, although the evidence on this point is not entirely clearcut, and vessels stored for much longer periods give satisfactory short term results.

Before the use of the homogenous arterial graft may become widespread, it will be necessary to solve the many practical problems related to the establishment of an artery bank. Obtaining suitable vessels is often difficult. The donor should be young and should have been in previous good health before succumbing to a rapid, noninfectious fatal episode. The graft must be taken aseptically within six hours of death. This combination of requirements is exceedingly difficult to fulfil, even in a large city. With current storage methods, the vessel is probably best used within a period of forty days, thus requiring a rather rapid turnover of vessels. Ways and means must be sought to develop an effective method of preservation for long periods. Rapid freezing technics and fixation with formaldehyde or alcohol are currently being investigated in several laboratories in this country.

The limitations on the use of homogenous arterial grafts have not yet been clearly delineated, particularly in regard to the size and length of the transplant. What is the smallest artery into which a graft may be successfully transplanted? Miller and his co-workers [4] have reported good function in the femoral artery of dogs. One of us (H. S.) has had gratifying results with the femoral artery in human patients. It would

3. Swan, H.; Robertson, H. T., and Johnson, M. E.: Arterial Homografts: The Fate of Preserved Aortic Grafts in the Dog, Surg., Gynec. & Obst. **90**:568 (May) 1950.

4. Miller, H. H.; Callow, A. D., and Welch, C. S.: The Fate of the Arterial Graft in Small Arteries, Bull. Am. Coll. Surgeons **35**:55 (Jan.) 1950.

seem probable that even smaller vessels, such as internal carotid, popliteal, or superior mesenteric arteries, could be successfully bridged. What is the maximum length of graft which can safely be used? This question has not been thoroughly studied experimentally. Gross [5] has used human aortic grafts from 2 to 6 cm. in length. In one of our patients with a femoral transplant, the segment was 7 cm. long. In the case reported in this communication, the aortic segment was 8 cm. long. Perhaps even longer segments might be successful. On the other hand, it is possible that there is a relation between the size of the vessel and the greatest usable length of graft.

CASE REPORT

W. M., a 16 year old school boy, was first admitted to the surgical service of the Colorado General Hospital on May 15, 1949, with a complaint of exertional dyspnea and easy fatigability of five years' duration. At the age of 11, on a routine physical examination, it was discovered that he had congenital heart disease, probably coarctation of the aorta. Three weeks later he became seriously ill and was hospitalized and treated for subacute bacterial endocarditis with sulfonamide drugs and with malarial fever therapy. After a two month stay, he was sufficiently improved to continue treatment on an outpatient basis, but a relapse occurred several months later, requiring rehospitalization. At this time he was treated with penicillin, which was continued for a period of several months. Since that time the patient had noticed dyspnea with mild exertion and occasional palpitation. In addition, dizzy spells with occasional fainting had occurred about twice a month for the past year. There had never been cyanosis or peripheral edema. Physical examination revealed a well developed but thin, intense white boy in no distress. The pulse rate was 130 and the blood pressure 175 systolic and 105 diastolic in both arms. No blood pressure or arterial pulsations could be obtained in the legs. The heart was not enlarged to percussion. A grade II blowing systolic murmur could be heard in the second interspace on each side of the sternum. In addition, there was a lower-pitched grade I systolic murmur over the apex. The aortic second sound was greater than the pulmonic second sound, although both were snapping in character. No cyanosis or edema of the extremities was evident. The day after admission, simultaneous direct arterial pressure recordings were made in the brachial and femoral arteries on the left. The brachial pressure was 175 systolic and 100 diastolic and the femoral pressure 93 systolic and 82 diastolic. Attempted intravenous angiocardiographic examination was unsatisfactory. The patient was discharged, to be readmitted during the school vacation for repair of his coarctation. Operation was performed on June 28, 1949. An adult type of coarctation, 2 cm. below the origin of the left subclavian artery, was found. Below the coarctation was an aneurysm of the aorta about 2 inches (5 cm.) in length and 2 inches in diameter, irregular in shape with areas of calcification within its walls. After mobilization of the various structures it did not appear to be safe to attempt resection of the coarcted area only with anastomosis between the aneurysm and the descending aorta above. Accordingly, a decision was made to resect the coarctation and the aneurysm a distance of about 2½ inches (6 cm.) and to bridge the gap with an arterial homograft. We had available an aorta which had been obtained aseptically three hours after the death

5. Gross, R. E.: Personal communication to the authors.

of a 14 year old boy who had been killed in an automobile accident fifty-two days previously. This had been stored in Ringer's plasma in the blood bank refrigerator. The length of the segment selected was 8 cm. The coarctation and aneurysm were now resected, and the gap was bridged by means of the graft. The proximal anastomosis was difficult because of the friable nature of the aorta at this point and had to be repeated. During the procedure there was one moment of brisk hemorrhage, but this was soon controlled, and the child left the operating table after the nine and one-half hour procedure in apparently good condition. The postoperative course was essentially uneventful with the exception of the behavior of the blood pressure. On the first postoperative day the pressure rose to the neighborhood of 200 systolic and 130 diastolic, where it remained with some fluctuations for a period of eight days. During this period, there were full bounding pulses palpable throughout both lower extremities. The urinary output was normal. Because of our concern with the possible fate of the graft in the face of this hyper-

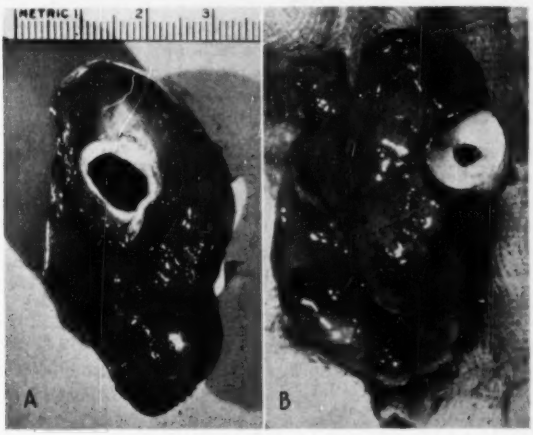

Fig. 1.—*A*, photograph of resected aortic aneurysm as seen from below. *B*, specimen as seen from above. The area of coarctation is just superior to the irregular aneurysm.

tension, the patient was given repeated large doses of tetraethyl ammonium chloride (etamon chloride®), but without noticeable effect on the blood pressure. During the next two weeks the blood pressure showed a slow trend toward normal levels, until at the time of discharge, four weeks after operation, the blood pressure in both arms and in the left leg was 135 systolic and 90 diastolic. In the six months that have elapsed since this operation, the patient has been feeling well, no longer observes exertional dyspnea and has had no further attacks of vertigo or fainting. Good femoral pulsations are still palpable, but the blood pressure in the arms has risen to about 160 systolic and 90 diastolic.

COMMENT

This human arterial homograft which had been in storage for fifty-two days at the time of transplantation has apparently remained

functional for a period of six months. At the present time the heart is normal in size on roentgen ray examination and there is no evidence of calcification appearing in the area of the transplanted vessel. The long term result, of course, cannot be predicted with accuracy.

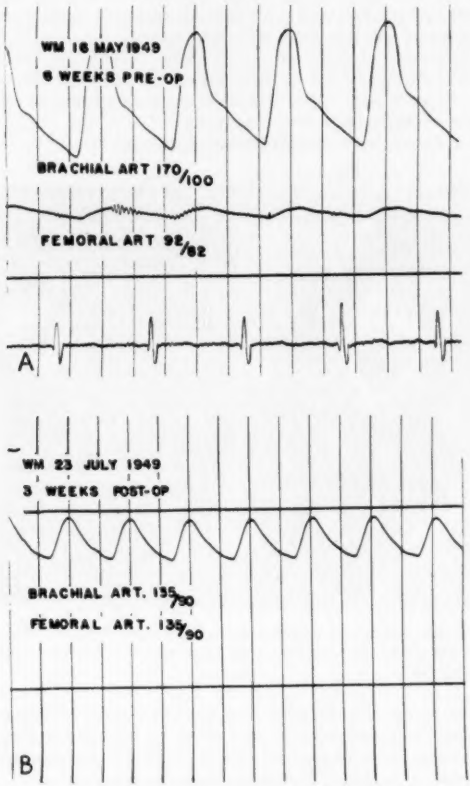

Fig. 2.—In (*A*) simultaneous strain gage intra-arterial pressure tracings of the left brachial and femoral arteries taken six weeks before operation are shown. The low femoral pulse and abnormal contour can be contrasted with the femoral artery tracing (*B*) taken three weeks after operation.

Of particular interest is the behavior of the patient's blood pressure since operation. The whole problem of the etiology of the hypertension

associated with coarctation is currently an unsettled one. Rytand [6] and Steele [7] have suggested that the diastolic hypertension in the lower extremities of many of these patients could not be explained on a mechanical basis and postulated interference with renal blood flow. Studies of renal blood flow, however, by Bing and others [8] and by Barker and Clark [9] did not substantiate any relation between hypertension in patients with coarctation and a renal mechanism. After repair of a coarctation alone, we [10] have observed an instability in several patients, with considerable fluctuation in blood pressure during the immediate postoperative period and a gradual tendency to stabilize within normal ranges. Strain gage intra-arterial pressure recordings taken preoperatively and postoperatively have shown that the femoral pulse contour and the radial-femoral ratio have reverted almost to normal by six weeks after operation. In this patient, however, after this return to normal, there has been a gradual increase to mildly hypertensive levels in the upper extremities so that during the past two months his blood pressure has been running in the neighborhood of 160 systolic and 190 diastolic, despite the fact that he now demonstrates markedly improved femoral pulse contour. It would appear to be difficult to explain these changes in blood pressure on a purely mechanical obstructive basis, and interference with the pressure-regulating mechanisms of the aortic arch, generalized increase in vascular tone or some renal mechanism must apparently be postulated. At the present time we have no explanation for this puzzling phenomenon.

SUMMARY

An adult type of coarctation of the aorta together with a mycotic aneurysm of the descending aorta in a 16 year old boy was resected and the gap in the aorta bridged by an 8 cm. human arterial homograft, which had been stored for fifty-two days. Six months after operation the vessel is apparently functioning well.

6. Rytand, D. A.: The Renal Factor in Arterial Hypertension with Coarctation of the Aorta, J. Clin. Investigation **17**:391 (Jan.) 1938.

7. Steele, J. M.: Evidence for General Distribution of Peripheral Resistance in Coarctation of the Aorta, J. Clin. Investigation **20**:473 (Sept.) 1941.

8. Bing, R. J.; Handelsman, J. C.; Campbell, J. A.; Griswold, H. E., and Blalock, A.: The Surgical Treatment and the Physiopathology of Coarctation of the Aorta, Ann. Surg. **128**:803 (Oct.) 1948.

9. Barker, H. G., and Clark, J. K.: Renal Function in Coarctation of the Aorta, Bull. Am. Coll. Surgeons **35**:53 (Jan.) 1950.

10. Grover, R. F.; Swan, H., and Maaske, C. A.: Intra-Arterial Pressures Before and After Aortic Resection for Coarctation in Man, Federation Proc. **9**:53 (March) 1950.

SURGICAL PROBLEMS ASSOCIATED WITH TREATMENT OF PATENT DUCTUS ARTERIOSUS

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AND
CARL B. DAVIS, JR., M.D.
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TWENTY-FOUR operations on 23 patients with patent ductus arteriosus form a small series. However, problems encountered in the care of these persons may be of interest. Their ages varied from 2 to 36 years, with two males and 21 females.

The diagnoses in these cases were made by Dr. Benjamin Gasul and his associates at the Cook County Children's and Mount Sinai Hospitals and by a number of cardiologists and internists at the Presbyterian Hospital. Five patients were subjected to cardiac catheterization by Dr. James Campbell in the Cardiovascular Laboratory of the Presbyterian Hospital. In all patients operated on to date for a patent ductus the pathologic process diagnosed was present and was found at the usual location, in the left mediastinum. Drs. Benjamin Gasul and Paul Casas have shown by retrograde angiocardiography that the aortic septal defects can now be differentiated from the patent ductus. Prior to this, diagnosis was possible at operation or autopsy.

The problems associated with surgical intervention for patent ductus arteriosus multiply many times with the advancing years of the patient. There is no doubt that the optimum time for operation is in early childhood while the vessels are elastic and vascular degenerative changes have not taken place and before bacterial aortitis and endocarditis have developed (fig. 1).

The first four patients operated on were children 3 to 8 years of age. Each had the ductus closed with three suture ligatures of heavy silk. The third patient, a girl of 7 years, had a recurrence (fig. 2) within two months. Since that time we have followed the advice of Dr. R. E. Gross [1] and changed the method to division of the ductus and suturing

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

1. (*a*) Gross, R. E., and Hubbard, J. P.: Surgical Ligation of a Patent Ductus Arteriosus: Report of First Successful Case, J. A. M. A. **112**:729 (Feb. 25) 1939. (*b*) Gross, R. E.: Experiences with Surgical Treatment in 10 Cases of Patent Ductus Arteriosus, J. A. M. A. **115**:1257 (Oct. 12) 1940; (*c*) Complete Surgical Division of The Patent Ductus Arteriosus: Report of 14 Successful Cases, Surg., Gynec. & Obst. **78**:36, 1944; (*d*) Complete Division for the Patent Ductus Arteriosus, J. Thoracic Surg. **16**:314, 1947. (*e*) Blalock, A.: Operative Closure of the Patent Ductus Arteriosus, Surg., Gynec. & Obst. **82**:113, 1946.

of the divided ends. A year after the recurrence referred to we were able to divide and suture the ends of the ductus. Thus in the 23 patients the results are excellent.

The chest is entered through the third interspace laterally, and the skin incision is placed below the breast. The mediastinal pleura (fig. 3)

Fig. 1.—Aneurysm of a patent ductus arteriosus removed from a 3 week old infant who died from a massive gangrene of the bowel secondary to a thrombosis of the superior mesenteric artery. It is possible that this thrombosis was secondary to an embolism that originated in the aneurysm.

is freed from the aorta for approximately 3 inches (8 cm.) from the first portion of the left subclavian artery and from the vagus nerve, which is gently retracted (to one side or the other as needed) with the

aid of a small Penrose drain. There have been no injuries to the vagus nerve or its recurrent branch. In the adult patients in whom the ductus is short and wide the aorta is freed so that an aortic clamp can be used if an emergency arises. The aortic clamp has been required in two cases (fig. 2 *C*), once during the division of the recurrent ductus and in a 24 year old female patient with a short, wide, sclerotic ductus. We have also found it is of great help to have the pulmonary artery well exposed for some distance on either side of the insertion of the ductus. The large pulmonary artery can then be encroached on in order to have adequate terminal cuffs to suture at the divided ends of the ductus.

The problems which we have encountered with the adult patients with patent ductus arteriosus are bacterial aortitis and endocarditis, severe hemorrhage at operation, postoperative hemorrhage, aneurysmal

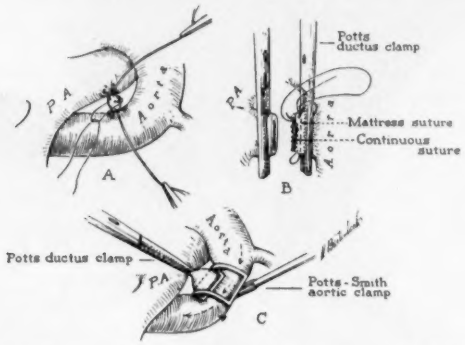

Fig. 2.—The three methods used in closing patent ductus are shown. The first four patent ductus were closed with three heavy silk suture ligatures as in *A;* one recurred and one year later the ductus was closed as in *C*. The procedure of choice, we believe, is that shown in *B*.

dilatation of the aorta at the site of the ductus and cardiac arrest followed by prolonged hypotension.

Hemorrhage occurred on two occasions, while the ductus was being freed in a 24 and a 36 year old woman. Both had thin-walled, sclerotic ductus which tore easily. In the first it was well controlled, with the Potts-Smith [2] aortic clamp on the aorta at the site of the ductus and the ductus then clamped at the pulmonary end. The second patient had an aneurysmal dilatation of the aorta to 3 inches (8 cm.) in width at the level of the ductus. None of the aortic clamps was of adequate size to apply, nor did we feel that this sclerotic fusiform swelling would tolerate

2. Potts, W. J.; Gibson, S.; Smith, S., and Riker, W. L.: Diagnosis and Surgical Treatment of Patent Ductus Arteriosus, Arch. Surg. **58**:612 (May) 1949.

clamping such as described by Crafoord.[3] Therefore, with digital pressure at the injured site, the rest of the ductus was freed and clamps applied to it, the ductus divided between the clamps and the ends sutured. During both of these procedures, blood was administered rapidly intravenously and a total of 6 and 8 pints (3,000 and 4,000 cc.), respectively, was necessary for blood replacement.

The only instance of postoperative hemorrhage which we have encountered occurred in the 24 year old patient mentioned above. At 8:00 p. m. on the day of operation the left side of the chest was found to be full of blood, and 1,800 cc. was removed. After this was removed and transfusions given, the patient's appearance improved for four hours,

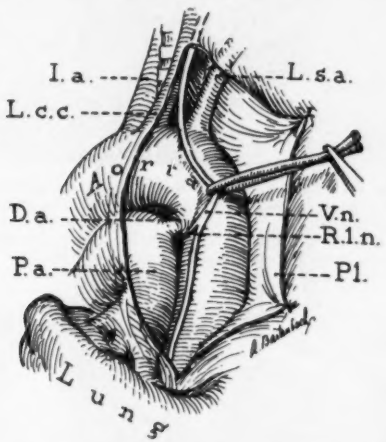

Fig. 3.—This drawing illustrates the exposure of the aorta, the vagus nerve with its recurrent branch, the pulmonary artery and the patent ductus arteriosus. The aorta is freed so that an aortic clamp can be applied if an emergency should arise.

when she again presented the picture of hemorrhage. She was taken to the operating room, where the wound was reopened and blood and blood clots removed. The bleeding was from many small vessels in the chest wall and the mediastinum. These vessels did not appear to have normal retractile qualities and were seen protruding from their various locations. Considerable time was required to accomplish hemostasis. An intercostal water-seal type of drainage was reestablished for three days. Aspiration of the pleural cavity was required four times. The patient has made a satisfactory recovery.

3. (*a*) Crafoord, C., in discussion on Gross [1d]; (*b*) British Heart J. **10**:71, 1948, 10-71.

Aneurysmal dilatation of the aorta occurred in a 30 year old man with associated bacterial endocarditis and aortitis and in the 36 year old woman referred to above, who also had considerable cardiac enlargement. This condition may be commoner than the literature indicates. Aneurysms of the ductus and pulmonary arteries are commonly referred to, but to date we have not encountered a discussion of a spindle or fusiform aneurysm of the aorta at the level of the ductus. In both of these patients the ductus was wide and at right angles with the aorta (fig. 4). Both aortic aneurysms were thick and sclerotic. The two patients have made excellent recoveries. During the seven months after

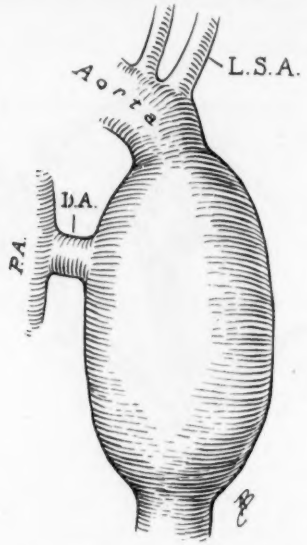

Fig. 4.—As illustrated, two aneurysms of the aorta have been encountered in adults of 30 and 36 years of age. Each ductus came off the aorta at a right angle, and the enlarged aorta was thickened and sclerotic. The ductus was divided and sutured in each case.

operation, the heart size in the 36 year old woman has decreased noticeably while the fusiform enlargement of the aorta has remained stationary (fig. 5).

Bacterial endocarditis [4] and aortitis occurred in a man of 30 years of age who had symptoms of intravascular infection for six months. He

4. Harrington, S. W.: Patent Ductus Arteriosus with Bacterial Endarteritis: Transpleural Ligation Through Posterolateral Approach; Report of Case, Proc. Staff Meet., Mayo Clin. **18**:217, 1943. Touroff, A. S. W., in discussion on Gross.[1d] Gross and Hubbard.[1a] Crafoord.[2b]

had known of his congenital heart condition for the greater part of his life. Positive blood cultures of Streptococcus viridans were found during the first few days of hospitalization. The preoperative management was conducted by Drs. Earl Gray and Marvin Dickey. Penicillin in the form of crystacillin, 300,000 units, was administered twice a day for six weeks. At the end of this time blood cultures showed no bacterial growth.

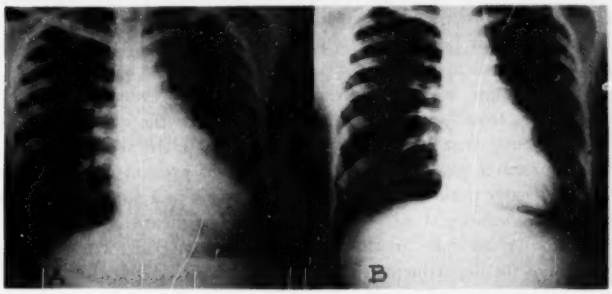

Fig. 5.—Roentgenograms of the chest (*A*) before and (*B*) six months after division and suture of the patent ductus in a 36 year old woman who had an enlarged heart and aneurysm of aorta revealed a smaller heart size and less pulmonary artery markings postoperatively while the enlarged aorta appears unchanged. Prior to operation she was markedly handicapped, and now she leads a normal life.

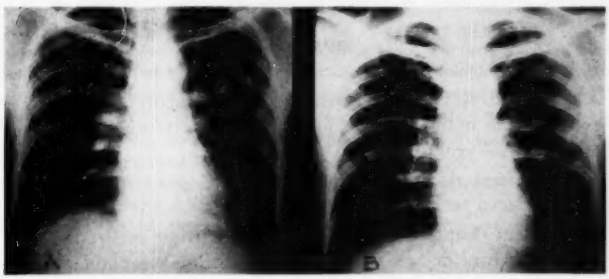

Fig. 6.—Roentgenograms of the 30 year old man with aneurysmal dilatation of the aorta and endocarditis. The blood cultures showed Streptococcus viridans on his admission. *A*, before surgery and, *B*, six months after division and suture of the patent ductus. The heart size is smaller, and the lungs are clearer of pulmonary artery shadows, but the enlarged aorta appears about equal in size, with a little less bulge in *B* than in *A*.

At operation a fusiform swelling of the aorta at the site of the ductus was found; it was approximately two and a half times the diameter of the aortic arch or the aorta distal to the enlargement. The ductus was 1¼ inches (3 cm.) long and ¾ inch (2 cm.) wide. The large ductus

showed no evidence of infection of its wall or lumen. The patient returned to work as a welder six weeks after operation. Six months after operation the heart size appeared normal. The enlarged aorta has not changed (fig. 6).

Cardiac arrest occurred while the ductus was being freed in a 22 year old woman. Rhythm was reestablished in less than a minute, but in spite of infusion of blood and an increase in oxygen administration, the blood pressure remained so low that the operation was halted for approximately an hour, after which it was felt safe to complete the procedure. Local application of 1 per cent procaine hydrochloride or 5 per cent cocaine, we believe, has been of aid in preventing these difficulties and is usually used before dissection about the ductus is begun. We have found that local infiltration of the intercostal nerves with 1 per cent procaine prior to spreading of the ribs prevents cardiac arrest during this early period. Most important, however, is a cooperative well trained anesthesiologist who will at all times be aware of the necessity of maintaining an open airway. It has been our good fortune to have the chiefs of the departments of anesthesiology personally administer the anesthetics at the three hospitals in which our work was done.

All patients have a water-seal type of chest drainage established at the end of the surgical procedure, and this catheter is usually removed 24 to 48 hours after the operation. There have been no pleural or mediastinal infections to date. One patient required postoperative aspiration of the chest, as stated previously.

SUMMARY

1. The diagnosis of patent ductus arteriosus can be accurately made.

2. Technical difficulties increase with advancing years, and we believe that the optimum time for surgical intervention is when the patient is 3 to 7 years of age.

3. The patent ductus in 4 patients was closed with three suture ligatures.

4. A patent ductus which recurred after a triple suture ligature in a child of 7 years of age was reoperated on one year after the first operation and the ductus divided and sutured.

5. Twenty patients' ductus were divided and sutured.

6. There were two severe hemorrhages in adults, 24 and 36 years of age, during operation. They were controlled, and adequate blood replacement made a satisfactory recovery possible.

7. One severe postoperative hemorrhage occurred within eight hours after surgical intervention, and bleeding was found occurring from many small nonretracted arteries and arterioles in the chest wall and the mediastinum.

8. A 30 year old patient, a man, with associated bacterial endocarditis and aortitis had negative blood cultures following intensive penicillin therapy; division and suturing of his ductus have restored him to normal activity.

9. Two aneurysms of the aorta, in adults 30 and 36 years of age, were associated with large wide ductus, which came off the aorta at a right angle. These were divided and sutured.

10. There were no injuries of the recurrent laryngeal nerve or the thoracic duct, nor was there empyema or any mediastinal infections among these patients. There were no deaths.

59 East Madison Street (Dr. Fell).

122 South Michigan Avenue (Dr. Davis).

DISCUSSION

OF PAPERS BY DRS. MAHONEY AND HOGG; SWAN AND OTHERS; FELL AND DAVIS

DR. WILLIS D. GATCH, Indianapolis: It is interesting that Osler, in the early editions of his "Practice of Medicine," mentions the occurrence of the condition discussed by Dr. Mahoney. Dr. Waltman Walters informs me that he heard Sir James Learmonth, professor of surgery at the University of Edinburgh, state that he had discovered that anastomoses between the splenic vein and the left renal vein are of constant occurrence and for that reason he never would do another splenorenal anastomosis. If that observation is true, I think we all ought to bear it in mind.

DR. HAROLD LAUFMAN, Chicago: My remarks concern the last statement that Dr. Gatch made. A number of years ago we placed cellophane bands about the superior mesenteric vein and artery and portal vein for gradual occlusion in order to observe some phenomena different from these being discussed today. Nonetheless, it was interesting that by so doing we caused no change in portal circulation so far as the nutriment coming up through the portal vein reached the liver despite complete occlusion of the portal vein. I have one slide to show this.

(Slide) Here you see the occlusion in the portal vein. This picture was taken after the cellophane band had been on for about four months. You see a rather extensive collateral circulation in the region of the capsule of the kidney, as well as many small vessels in the peritoneum, so that actually the portal system of the liver does fill. I think that explains, too, the lack of nutritional deficiencies in the first child whom Dr. Mahoney showed. Gradual occlusion of the portal vein allowed collateral circulation to form. The appearance of that child was not like that of an animal with an Eck fistula.

DR. WILLIS J. POTTS, Chicago: Drs. Fell and Davis have given a sound appraisal of the status of patent ductus surgery. It seems that the cardiologists have agreed that patent ductus should be operated on, but we as surgeons have not come to complete agreement on the method of procedure.

As you know, Dr. Gross was fortunate in getting a ligature around the first ductus but later found that simple ligations were followed by recurrences. He then adopted the procedure of division and suture. There is still some disagreement about this subject. It is our feeling that all patent ductus should be divided and sutured. I believe there will be fewer complications with division than with ligation, not only at operation but after operation.

(Slide) A couple of years ago, because of the fear that a little Halsted clamp would slip off the stump of a ductus, these clamps were devised. As you know, these multiple teeth, forty to an inch, embed themselves in the adventitia, and, as Dr. Davis has said, they will not slip and will not injure the vessel.

(Slide) This is the artist's drawing of the teeth, which are fine, close together and distribute the pressure equally to all parts of the ductus wall.

(Slide) We open the chest through the fourth interspace in the posterior lateral position rather than the third. I think that is purely a matter of individual variation. Two points are of prime importance in the technic of division and suture: complete separation of the pericardial lappet from the ductus and painstakingly thorough dissection of the ductus from all surrounding structures. If the pericardium is not taken off completely, the teeth of the clamp will embed themselves in it and allow the stump of the ductus to withdraw and roll out. We had that happen in two early cases. The stump of the ductus on the pulmonary side rolled out partially because we had caught the pericardium in the clamp.

Not infrequently, one will find in a child 12 to 13 years of age a ductus of 1 cm. or more in diameter and seemingly not more than a millimeter or two in length. As the tissue is dissected out in this area and as the pericardium is taken off, the ductus lengthens. One can be crowded toward the aortic side and the other on the pulmonary side, invariably allowing 4 to 5 mm. between the two clamps. That length is sufficient for proper suture. We use a to-and-fro mattress suture plus an over-and-over suture.

In the early days we ligated 20 ductus. As far as we know there has been no recurrence, but we do not like the idea of all that foreign material resting against the bronchus. Since we have used these clamps we have divided and sutured 90, with trouble in two cases and for the same reason.

We did not dissect off the pericardial lappet sufficiently far on the pulmonary side, and part of the ductus stump slid out of the clamp. There has been no mortality in either group.

Dr. Gordon Murray, Toronto, Ontario: I should like to make a comment on Dr. Davis' paper regarding the method of dealing with the ductus. I am not refuting anything that was said, and my purpose in saying this is to show that there are different methods of accomplishing the same thing. My experience is based on ligation only in over 80 cases of ductus. My feeling is that, with no recurrences in the 80 cases, ligation is a much simpler method of dealing with it than is division and suturing. I think when you have dissected it out, clamped it off and begun to suture it, you have undertaken a big job. As already recounted here, there are some disasters or difficulties encountered. There have been no fatalities, but there are difficulties.

Ligation is considered a relatively minor procedure. With no recurrences in over 80 patients, I am in favor of tying off, with at least five ligatures. This puts more material against the bronchus than Dr. Potts likes, but there have been no infections of the wounds, no fatalities, no recurrences and no complications.

Regarding the paper by Dr. Swan on aortic transplants, my experience is limited, but I have used these, and I speak mostly from my experience with transplanting veins into arteries. I have transplanted a venous graft up to 4½ inches (11 cm.) in length that I know is working now, fifteen years later. I have another one of about 3 inches (8 cm.) in the femoral artery that is easily accessible and has been working well for some time. There is no dilatation and no degeneration that one can feel, and it seems normal in every respect.

Regarding the transplantation of the aorta itself, not very long ago a patient was referred who had an enlarging abdominal aneurysm. She was a woman in her late fifties, and under observation it was felt that this aneurysm was going on to perforation. We were concerned with whether it was up above the renal vessels or not, and it was found to end just above the bifurcation of the aorta.

We put in an aortic graft 4 inches (10 cm.) in length, which went off perfectly and the patient was well afterward. The pulsation in the legs was excellent, and we were satisfied with the result. However, unfortunately she died soon afterward. We got the specimen, and it looked good in all respects.

The pathologist cut sections of the anastomosis, and his comment was that the section of the graft looked healthy, whereas that of the patient's aorta looked badly. That is explainable on the basis that the patient had an arteriosclerotic aneurysm, but the suture lines were good, everything looked well and there was no thrombosis. If something else had not happened (the cause of death was not discovered), the end result might have been good.

DR. CARL B. DAVIS JR., Chicago: I should like to thank Dr. Potts for his remarks. Dr. Murray's series is very commendable, and he certainly is keeping good company with Dr. Blalock. We still feel that we shall continue to divide the ductus and hope that we shall not have any severe difficulties.

EFFECT OF BETA IRRADIATION ON GASTRIC ACIDITY

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WINSTON R. MILLER, M.D.
AND
DEMETRIUS G. JELATIS, Sc.D.
RED WING, MINN.

THIS PAPER is a preliminary report of studies still in progress on the reduction of gastric acidity in the dog by the use of radioactive phosphorus, known as P^{32}. The basic purpose is to determine whether beta irradiation from P^{32} might be effectively and safely used in the treatment of peptic ulcer by reducing gastric secretion.

Several workers [1] have produced a decrease in acidity for varying intervals with the use of gamma rays. Palmer and Templeton [2] in 1934 reported 100 cases of peptic ulcer treated with roentgen rays in which they irradiated the stomach anteriorly and posteriorly over a period of ten to twelve days. They reported a definite decrease in gastric acidity, which varied in extent and duration.

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

From the Interstate Clinic (Dr. Hedin and Dr. Miller) and the Central Research Laboratories, Inc. (Dr. Jelatis).

1. Brick, I. B.: Radiation Effects on the Human Stomach, Rev. Gastroenterol. **13**:363-370, 1946. Dawson, A. B.: Histological Changes in Gastric Mucosa (Pavlov Pouch) of the Dog Following Irradiation, Am. J. Roentgenol. **13**:320-328, 1925. Engelstad, R. B.: The Effects of Roentgen Rays on the Stomach in Rabbits, ibid. **40**:243-263, 1938. Hueper, W. C., and de Carvojal-Ferero, J.: The Effects of Repeated Irradiation of the Gastric Region with Small Doses of Roentgen Rays upon the Stomach and Blood of Dogs, ibid. **52**:529-534, 1944. Ivy, A. C.; McCarthy, J. E., and Orndoff, B. H.: Studies on the Effect of Roentgen Rays on Glandular Activity: Effect of Exposure of Abdominal and Thoracic Areas to Roentgen Rays on Gastric Secretion; Roentgen Cachexia J. A. M. A. **83**:1977-1984 (Dec. 20) 1924. Levin, E.; Hamann, A., and Palmer, W. L.: The Effect of Radiation Therapy on the Nocturnal Gastric Secretion in Patients with Duodenal Ulcer, Gastroenterology **8**:565-574, 1947. Palmer, W. L.; Kirsner, J. B., and Nutter, P. B.: Spontaneous Variations in Gastric Secretion in Response to Histamine Stimulation, Am. J. Digest. Dis. **7**:427-430, 1940. Palmer, W. L.: Peptic Ulcer and Gastric Secretion, Arch. Surg. **44**:452-472 (March) 1942. Platt, W. R.: Effect of Radioactive Phosphorus (P^{32}) on Normal Tissue, Arch. Path. **43**:1-14 (Jan.) 1947. Portis, S. A., and Ahrens, R.: The Effects of the Shorter Wave-Length Roentgen Ray on the Gastric Secretion of Dogs, Am. J. Roentgenol. **11**:272-280, 1924.

2. Palmer, W. L., and Templeton, F.: The Effects of Radiation Therapy on Gastric Secretion, J. A. M. A. **112**:1429-1434 (April 15) 1939.

In 1942 two New Zealand investigators, Jenkins and McGeorge,[3] using gamma rays, placed radium needles in a rubber-covered tube and passed it into the stomach under the fluoroscope. The radium was allowed to remain in place for four to five hours daily until 2,500 milligram hours was given. They reported a reduction in gastric acidity in 13 of the 14 peptic ulcers treated.

Simon [4] in 1949, using beta particles of P^{32}, studied the effect on gastric acidity in Heidenhain pouches of dogs. He used a rubber bag which had been sprayed with rubber cement. Short cotton fibers were made to adhere to the cement, giving the balloon a feltlike covering. This absorbent material was dipped in a solution of P^{32} and allowed to dry. As much as 25 millicuries of P^{32} was absorbed uniformly on the flocculated surface of the balloon. The balloon was covered by a condom, reinflated to 50 cc. and placed in the Heidenhain pouches of 5 dogs. Simon reported a decrease in total secretion as well as a decrease in quantity and concentration of hydrochloric acid in the pouches of all the dogs.

Radioactive phosphorus was first used in 1936. At that time it was rendered radioactive by the cyclotron. P^{32} has been used extensively in cases of blood dyscrasias and of malignant neoplastic disease.[4a] The isotope which was used in this work has a half life of 14.3 days and was obtained through the Atomic Energy Commission from the Oak Ridge Pile.

METHOD

In the present studies, the entire gastric mucosa was irradiated with beta rays from radiophosphorus (P^{32}) in the form of an aqueous solution of activated potassium dihydrogen phosphate which was pumped into a condom in the dog's stomach.

Ten dogs were used, of which 5 were littermates. A rubber balloon attached to the end of a large rubber catheter was passed into the stomach of each dog that had been anesthetized with veterinary pentobarbitol sodium (nembutal sodium®). Under the fluoroscope, the balloon was distended with 20 per cent sodium bromide solution until the stomach wall was sufficiently distended to iron out the mucosal rugae (400 to 700 cc.) (fig. 1). The sodium bromide solution was then siphoned off and replaced with an equal quantity of the radioactive phosphorus solution. The radiation dose given each dog was determined by the length of time the radioactive solution was left in the stomach. The doses of beta irradiation varied from 250 to 10,000 rep [5] in the 10 dogs.

3. Jenkins, J. A., and McGeorge, M.: Control by Radium for Gastric Acidity, Arch. Int. Med. **70**:714-721, (Nov.) 1942.

4. Simon, N.: Suppression of Gastric Acidity with Beta Particles of P-32, Science **109**:563-564, 1949.

4a. Reinhard, E. H.; Moore, C. V.; Bierbaum, O. S., and Moore, S.: Radioactive Phosphorus as a Therapeutic Agent: A Review of the Literature and Analysis of the Results of the Treatment of 155 Patients with Various Blood Dyscrasias, Lymphomas, and Other Malignant Neoplastic Diseases, J. Lab. & Clin. Med. **31**:107-215, 1946.

5. Rep indicates roentgen equivalent physical; 1 rep is that dose of ionizing radiation which produces energy absorption of 83 ergs per cubic centimeter of tissue.

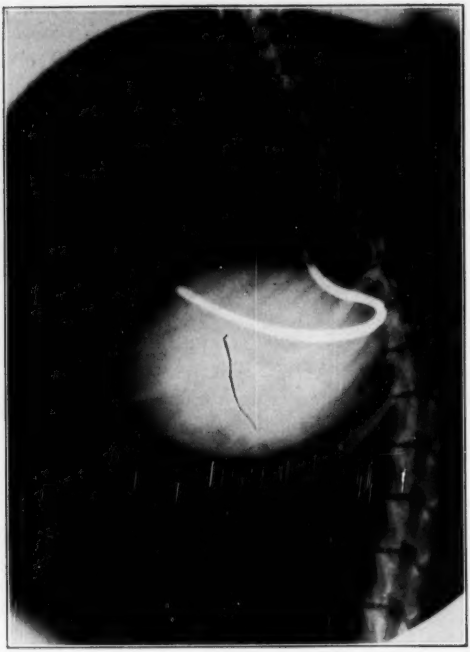


Fig. 1.—Roentgenogram of dog's stomach distended with sodium bromide to determine capacity of stomach. The sodium bromide is replaced with an aqueous solution of P^{32}. By this method the mucosa is ironed out, allowing the irradiation to come in contact with the greatest surface of gastric mucosa.

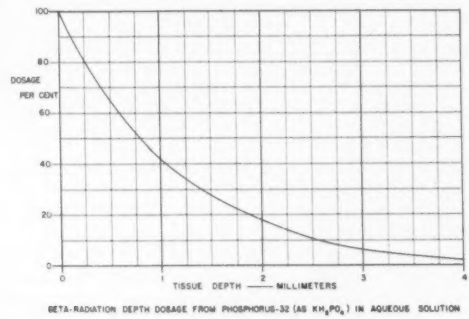


Fig. 2.—Graph showing the decrease in beta irradiation as it penetrates tissue.

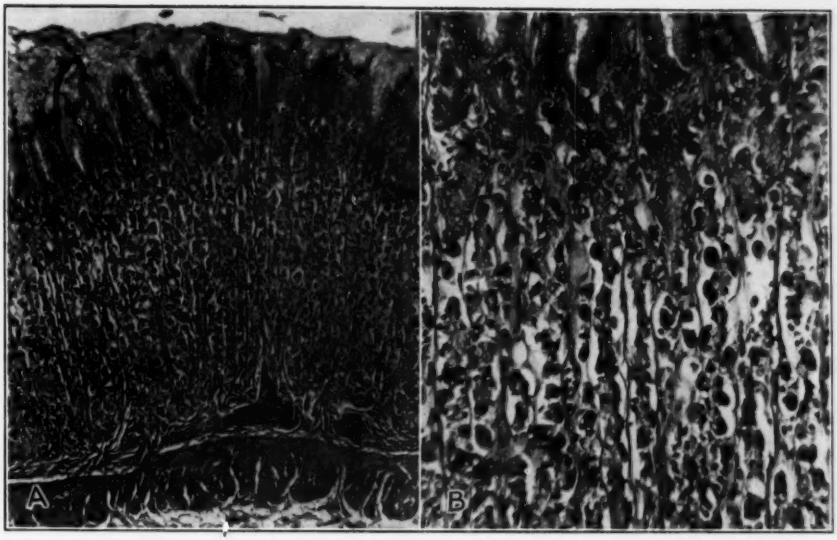


Fig. 3.—Sections of the normal gastric fundus of a dog. *A*, × 65; *B*, × 150.

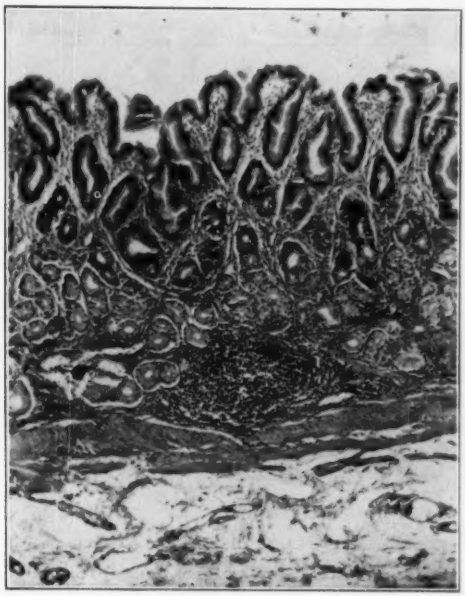


Fig. 4.—Section of the normal gastric antrum of a dog; × 65.

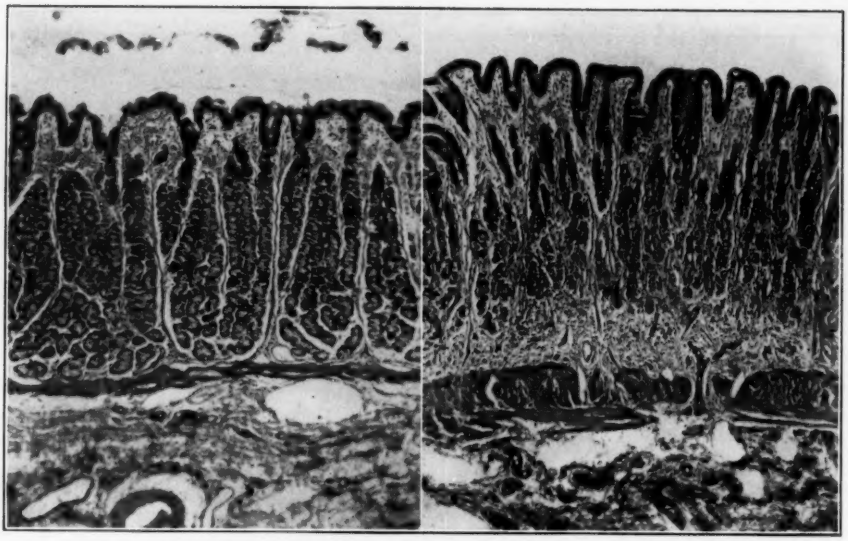


Fig. 5.—*A*, section of the gastric fundus in a dog irradiated with 2,000 rep. There is a slight decrease in the parietal cells in the gastric glands; × 65. *B*, section of the gastric fundus in a dog irradiated with 5,600 rep. There is a definite decrease in the number of gastric glands. The effect appears to be more marked on the parietal cells than on the chief or zymogenic cells; × 65.

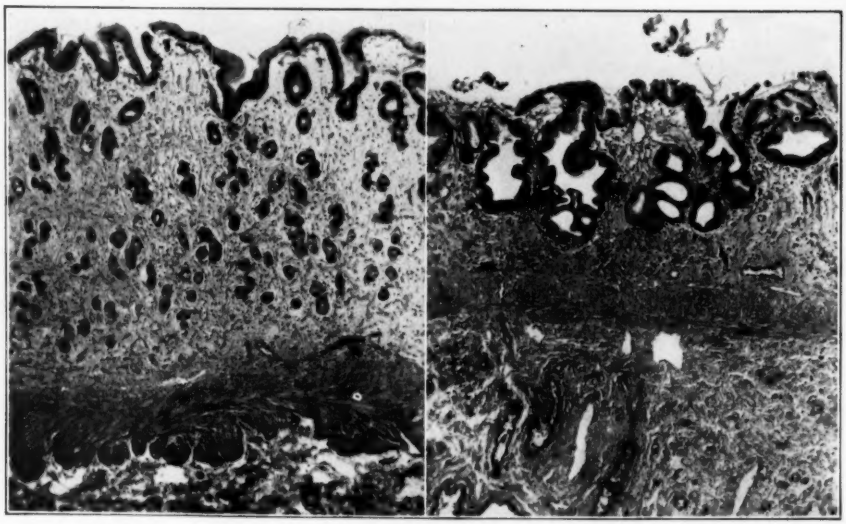


Fig. 6.—*A*, section of the gastric fundus in a dog irradiated with 8,100 rep. There is a marked decrease in the gastric glands. Practically all the parietal cells are absent; × 65. *B*, section of the gastric fundus in a dog irradiated with 10,000 rep. There is almost complete absence of gastric glands and a definite narrowing of the depth of the gastric mucosa; × 65.

The effective penetration of the beta radiation from this solution was determined by using aluminum absorbers, with the following results: The dosage rate at a depth of 1 mm. is 40 per cent of the maximum at the surface; at a depth of 3 mm. the rate is only 7 per cent of that at the surface (fig. 2). Thus the effects of irradiation are limited to the desired tissues, with practically no effect on surrounding tissues.

Determinations of gastric acidity were made on fasting specimens before and after injection of 0.5 to 1.0 mg. of histamine in the form of histamine acid phosphate. The arithmetic mean of several determinations before irradiation was calculated to indicate the normal acidity potential of each dog. After irradiation, gastric

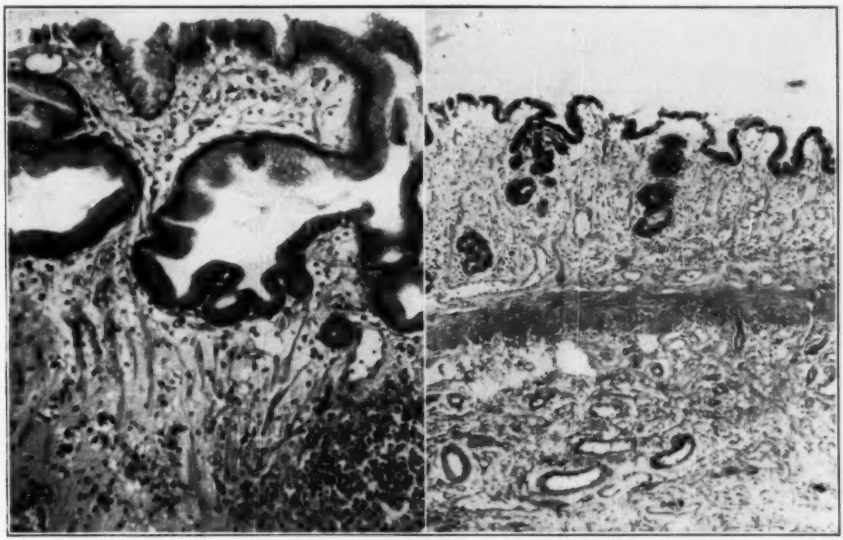


Fig. 7.—*A*, section of the gastric fundus in a dog irradiated with 10,000 rep. Here it is possible to see a few residual gastric glands, but the connective tissue supporting the glands still remains, and in certain areas cell shadows are present. The lymphocytic elements in the mucosa appear not to have been affected by the irradiation. The surface epithelium is shown to be intact. In view of the degree of damage to the gastric glands, it would seem likely that after irradiation the surface of the epithelium may have been almost completely destroyed but after a period of time it has regenerated; × 150. *B*, section of the gastric antrum in a dog irradiated with 10,000 rep. Here is a marked destruction of the gastric glands. While a few remain, most of them have been destroyed. Only in the higher dosage does the antrum appear to have been affected; × 65.

analyses were made at four to ten day intervals. At the time of writing, the total interval after irradiation is ninety-seven days.

Biopsies of the fundus and antrum of the stomach of each dog were taken several weeks before irradiation (figs. 3 and 4) and again six weeks after irradiation, and the histologic changes were studied (figs. 5, 6 and 7).

Body weight, red blood cell count, white blood cell count, differential count and blood sedimentation rates were determined at intervals before and after irradiation.

RESULTS

In 1947, when this work was started, beta irradiation of the stomach had not been reported in the literature. Because of this, it was necessary

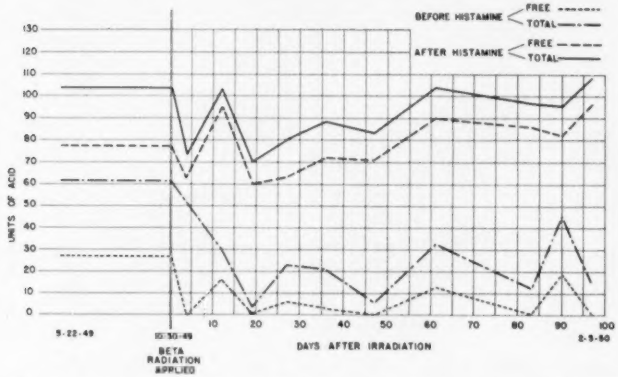


Fig. 8.—Gastric acidity determinations in dog no. 5 before and after irradiation with 2,000 rep for two hours.

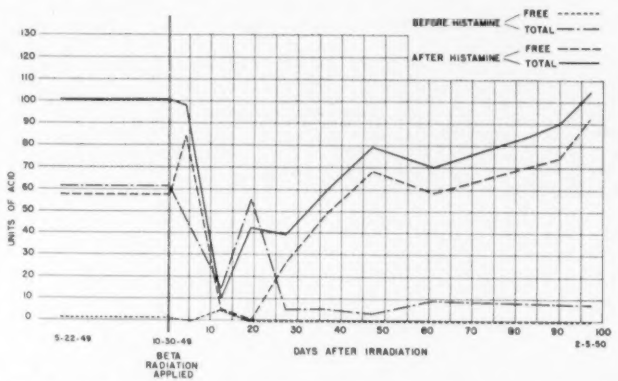


Fig. 9.—Gastric acidity determinations in dog no. 4 before and after irradiation with 5,600 rep for five and a half hours.

to begin with small amounts of irradiation and increase the dosage until there were some demonstrable changes in the gastric acidity. Such changes were then correlated with the histologic changes in the biopsies of the antrums and fundi of the stomachs. The first 5 dogs irradiated

were arbitrarily given P^{32} in doses ranging from 250 to 1,500 rep. Gastric secretion was not significantly altered by these smaller dosages. In the 2 dogs receiving 1,200 and 1,500 rep, there was a slight temporary decrease in gastric acidity from the fourteenth to the twenty-

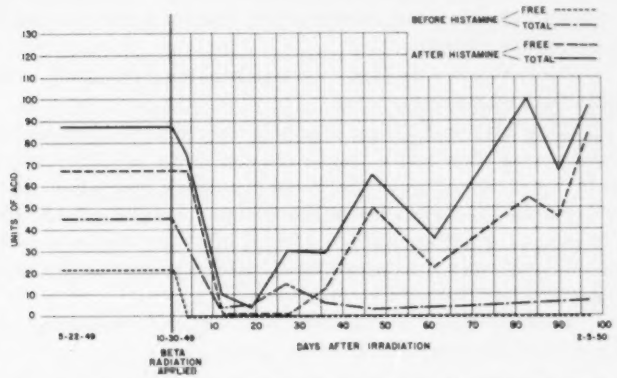


Fig. 10.—Gastric acidity determinations in dog no. 2 before and after irradiation with 8,100 rep for eight hours.

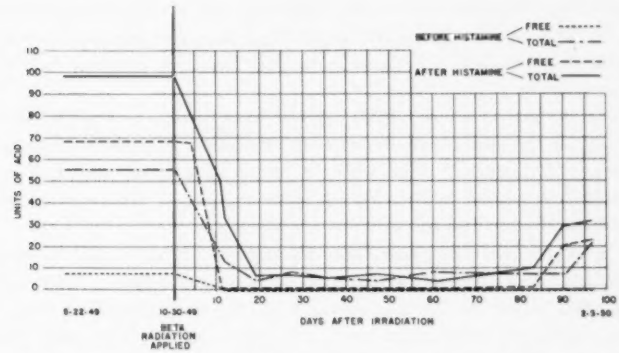


Fig. 11.—Gastric acidity determinations in dog no. 3 before and after irradiation with 10,000 rep for 10.3 hours.

eighth day after irradiation. Histologic changes showing a small amount of cellular destruction in the gastric mucosa correlated with these transitory changes in gastric acidity. However, after thirty days the gastric acidity had returned to the normal levels in all 5 dogs.

In the second group of 5 dogs, larger doses of P^{32} were used and significant changes occurred in gastric acidity (figs. 8, 9, 10 and 11) and in the histologic picture after irradiation. The dosages in this group ranged from 2,000 to 10,000 rep. These changes are best shown in the accompanying graphs and histologic sections. The changes are in direct proportion to the amount of P^{32} irradiation used and can be summarized as follows:

1. The thickness of the gastric mucosa decreased progressively as the irradiation dosage increased.

2. When 2,000 to 8,100 rep doses of P^{32} were used to irradiate the gastric mucosa, there was a definite decrease in the number of gastric glands in the fundus. After the 10,000 rep dosage only a few gastric glands remained and only a few isolated clumps of parietal and chief cells were seen. The antrum was less affected by the irradiation than the fundus. Only when the largest dose (10,000 rep) was used was the cellular structure destroyed in the antrum.

3. After high doses of irradiation were used, only supporting connective tissue elements remained in the gastric glands.

4. The surface epithelium appears unaltered in the postirradiation sections of the gastric mucosa. In view of the striking changes which have occurred in the gastric glands, it seems probable that the surface epithelium sloughed off after the irradiation and completely regenerated.

5. The decrease in gastric acidity, quantitatively and qualitatively, could be strikingly correlated with the histologic sections and the amount of irradiation used.

In the dog in which 10,000 rep was used there was a slight return of acid on the ninety-seventh day after irradiation. The partial regeneration of the gastric mucosa with the return of a small amount of acid would seem to be a desirable situation in view of the close relation between achlorhydria and carcinoma of the stomach.

6. There was a transitory loss of weight in all the 5 dogs receiving the larger doses during the four weeks following irradiation. However, after this period, the loss was regained and the weight remained normal. Red, white and differential blood cell counts and sedimentation rates remained the same, being unaltered by irradiation.

SUMMARY AND CONCLUSIONS

1. The stomachs of 10 dogs were exposed to various doses of beta irradiation from P^{32} to determine the effect on gastric acidity.

2. The capacity of the distended dog's stomach was determined, and a balloon filled with radiophosphorus solution was allowed to come

in contact with the ironed-out gastric mucosa for various lengths of time.

3. A rather striking correlation was obtained between the changes in gastric acidity and the histologic changes in the gastric mucosa after various doses of P^{32}.

4. From the data at hand, it appears that a dosage of the order of 10,000 rep produces a marked reduction in gastric acidity for a prolonged time without complete achlorhydria.

5. Further studies are in progress to determine whether this method of reducing gastric acidity might be safely applied to the treatment of peptic ulcer.

Dr. John F. Noble, Pathologist, St. John's Hospital, Red Wing, Minn., assisted in interpreting the histologic studies made during the course of this work.

The P^{32} used in this investigation was supplied by the Oak Ridge National Laboratory on allocation from the Isotope Division, United States Atomic Energy Commission.

TREATMENT OF PERFORATED PEPTIC ULCERS

WILLIAM T. McELHINNEY, M.D.
AND
M. M. ZINNINGER, M.D.
CINCINNATI

DURING the years 1935 to 1949 inclusive, 428 patients with acute perforated peptic ulcer were treated at the Cincinnati General Hospital. This report is concerned chiefly with the 128 patients who were seen during the past five years and who received penicillin as a part of their treatment. The other patients have been reported on previously and are used for comparison of the results of treatment.[1] The purpose of this analysis is, first, to determine whether immediate operative treatment of peptic ulcer, after the use of proper supportive measures, is justifiable in the face of the remarkable results which have been reported with the nonoperative method of treatment and, second, to consider briefly the question of immediate gastric resection in selected cases of perforated ulcer.

The treatment of acute perforated ulcer at the Cincinnati General Hospital, as developed over the past fifteen to twenty years, has been operation, with simple closure of the ulcer as soon as the condition of the patient warrants it. As carried out at present, the procedure is as follows: As soon as a tentative diagnosis of acute perforation of an ulcer is made in the hospital receiving ward, a Levin tube is passed into the stomach and continuous suction is started. Penicillin is given intramuscularly, and fluids are administered intravenously if there is shock or dehydration. After these procedures are completed and if the patient is in sufficiently good condition, roentgenograms of the abdomen in the semierect or the lateral decubitus position are made in order to determine whether there is free air in the peritoneal cavity. The patient then goes to the ward or to the operating room. The operative closure of the perforation is not done until the circulation has been stabilized. Cyclopropane or spinal anesthesia is used. Blood transfusion may be necessary to maintain adequate circulation in patients in

Read at the Seventh Annual Meeting of the Central Surgical Association, Chicago, Feb. 17, 1950.

From the Department of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital.

1. McElhinney, W. T., and Holzer, C. E.: Factors Influencing Mortality from Acute Perforated Ulcers, Surg., Gynec. & Obst. **87**:85-92, 1948.

whom perforation has been present for over twelve hours. The perforations are closed by inverting the edges with silk sutures and tying a tag of omentum into the long ends of the sutures. In some cases in which closure is difficult and omentum is not available, a fold of stomach is pulled over the perforation. Until 1946, through and through silver or steel wire sutures were used for closure of the wound because of the high incidence of wound infection and evisceration. Since that time, many of the wounds have been closed with buried steel wires. The abdominal cavity is not drained. Postoperatively, Wangensteen suction is used for an average of two days, during which time the patients are maintained on intravenous therapy. Penicillin has been administered in various treatment schedules, from 3,000 units every three hours to the present schedule of 100,000 units twice a day. It is given for at least six days.

During the past five years, 122 patients with acute perforated ulcer have been operated on, with 5 deaths.

TABLE 1.—*Cases of Perforated Peptic Ulcer at the Cincinnati General Hospital for 1945 to 1949, Inclusive*

	Patients	Deaths	Mortality, %
Operated on	122	5	4
Not operated on	6	3	50
	128	8	6.2

30% of the patients were operated on over 12 hours after perforation

Six other patients were treated without operation, with 3 deaths. Among the patients operated on the 5 who died are briefly described in order to indicate the types of cases included in this series. Three of the 5 deaths involved patients who had incurable diseases, recognized preoperatively. The first was a 67 year old man who was admitted in shock. A diagnosis of perforated peptic ulcer was made, with evidence of free air under both sides of the diaphragm. After treatment for shock, a prepyloric ulcer was closed, twelve hours after the perforation. The patient suddenly collapsed and died forty-eight hours postoperatively. Autopsy revealed a massive gastrointestinal hemorrhage. The second patient was a 53 year old Negro woman in whom an anterior duodenal ulceration was closed six hours after perforation. She died suddenly on the fifth postoperative day. Autopsy revealed a ruptured aorta and hemothorax involving the left side. The third patient was a 36 year old man with far advanced tuberculosis. An ulcer on the anterior duodenum was closed twelve hours after perforation. Critically ill before the operation, this patient had an extremely stormy course and died on his fourteenth postoperative day. Autopsy revealed

a second perforation below the first. The first had been adequately closed. There was evidence of leakage from the second perforation, with peritonitis, in spite of continuous suction and chemotherapy. The fourth patient was a 55 year old Negro with aortic insufficiency and Laennec's cirrhosis. A large prepyloric perforation was closed with the patient under local anesthesia twelve hours after perforation. The wound disrupted on the sixth postoperative day, and the patient died twenty-four hours thereafter. The fifth patient was a 58 year old man with severe cirrhosis and free abdominal fluid, who had been bedfast before his admission to the hospital. A large prepyloric ulcer was closed sixteen hours after perforation, with the use of local anesthesia. The patient died on the sixth postoperative day. Only 1 of these 5, in whom ulcers were closed within twenty-four hours after perforation and who subsequently died, was not suffering from a critical disease in addition to the perforated ulcer. In 26, or 21 per cent, of the cases, the ulcers were closed twelve hours or more after the perforation. This percentage

TABLE 2.—*Cases of Perforated Peptic Ulcer at the Cincinnati General Hospital for 1945 to 1949*

A. Operation within 12 hours after perforation		2 deaths
1—Hemorrhage from ulcer	autopsy	
1—Ruptured thoracic aneurysm	autopsy	
B. Operation from 12 to 24 hours after perforation		3 deaths
1—Far advanced pulmonary tuberculosis, with second perforation postoperatively	autopsy	
2—Cirrhosis of liver, severe, with ascites	.....	

is slightly higher than that in Baritell's[1a] series of perforations, in which 18 per cent of the patients were operated on within twelve hours after perforation.

It is apparent that the mortality rate among patients with perforated peptic ulcers treated by the operative method approaches 1 per cent if one excludes those cases in which death is not attributable entirely to the perforation. Perforated ulcers are not uncommon in patients suffering from other serious diseases, such as cirrhosis, tuberculosis and carcinomatosis. The results of treatment in this type of patient are always poor. Examination of the charts of patients who were reasonable risks and who did not have serious associated diseases shows that among 118 who underwent operation there was 1 fatality.

The question of treatment of patients who are seen twenty-four hours or more after perforation has occurred remains a serious problem. The condition of these patients on their admission to the hospital is variable, some being in coma with widespread peritonitis while in others the perforation has sealed off after relatively little leakage or extensive

1a. Baritell, A. L.: Perforated Gastroduodenal Ulcers, Surgery **21**:24-33, 1947.

infection. For patients with a generalized infective peritonitis, the treatment is an individual problem and consists of the administration of massive doses of chemotherapeutic drugs, blood transfusions, Wangensteen suction and the judicious drainage of accumulations of peritoneal fluids. In our hands, operative intervention to close the perforation has not influenced the mortality rate.

Taylor [2] recommended the nonoperative method of treatment of perforated peptic ulcer in September 1945. He supported his views by reporting 28 cases, with 4 deaths, 3 of which he did not attribute to the form of treatment. He did not advocate this method for all cases of perforation, such as delayed cases with infective peritonitis or those in which there had been gross flooding of the peritoneal cavity. His decision to intervene surgically was based on the degree of leakage that had taken place. In a recent personal communication, he described another group of patients treated without operation, which will be reported soon. Bingham,[3] in Canada, reported 62 cases, with a mortality of 11.3 per cent. His cases included those of Taylor. Seeley [4] reported

TABLE 3.—*Nonoperative Mortality Rates*

	Number of Cases	Mortality, %	Year
Taylor [2]	28	14.3	1946
Bingham [3]	62	11.3	1948
Seeley [4]	78	0	1949
Lane	70	1.4	1949

34 cases, with no deaths, and in a recent personal communication listed a series of 78 cases without a death. Dr. John Lane, of the United States Public Health Department, is said to have a series of 70 patients treated in this manner, with 1 death.

The nonoperative method has not been used at the Cincinnati General Hospital on patients who have had perforations less than twenty-four hours, because of the following reasons:

1. It has been our impression that perforated ulcers treated by operative closure and penicillin do as well or better than those treated by the nonoperative method. When Taylor adopted the nonoperative method of treatment, he did so because the operative mortality in his hospital was 18 per cent, with 14 deaths in 77 cases. At the Cincin-

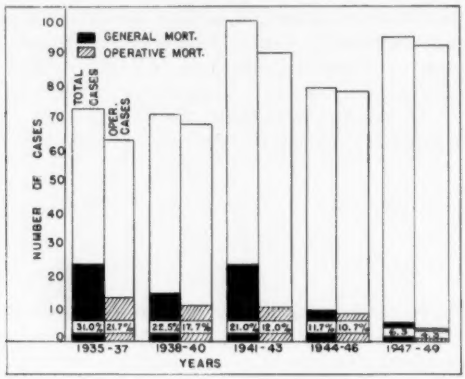
2. Taylor, H.: Perforated Peptic Ulcer Treated Without Operation, Lancet **2**:441-444, 1946.

3. Bingham, D. C.: The Treatment of Acute Perforated Peptic Ulcer, Canad. M. A. J. **58**:1-5, 1948.

4. Seeley, S. F.; Hogan, E.; Henry, J. R., and Bertram, H. F.: Nonoperative Treatment of Perforated Duodenal Ulcer, Bull. U. S. Army M. Dept. **9**:124-130, 1949.

nati General Hospital the total mortality at that time (1941 to 1943) was 21 per cent, with an operative mortality of 12 per cent. When Taylor reported a reduction of the mortality rate by adoption of the nonoperative method of treatment, our over-all mortality (1944 to 1946) was 11.7 per cent, with an operative rate of 10.7 per cent. This has since been reduced (1945 to 1949) to a total mortality of 6 per cent, with an operative rate of 4 per cent (see chart).

2. We have been unable to assess from clinical or physical findings how much gross contamination has occurred. It has been our experience and that of others that there are no criteria to determine how much leakage has occurred. We have seen patients with marked abdominal symptoms on physical examination in whom there was only the slightest



Mortality of perforated peptic ulcer at the Cincinnati General Hospital, 1935 to 1949.

contamination at operation. On the other hand, in a number of patients who were diagnostic problems because of the meager abdominal findings there was gross soiling of the abdominal cavity at operation. The fact that the patient has not eaten for one hour prior to perforation does not mean that the stomach will be empty. One of Bingham's criteria for use of the nonoperative method was the determination of whether the patient had eaten in the previous hour. He recommended surgical intervention in all cases in which perforation had occurred within one hour after eating.

3. The nonoperative method of treatment does not contribute to an accurate diagnosis of other conditions causing acute abdominal symptoms. The surgical condition of the abdomen causing the most confusion is acute appendicitis. During the last five years in this hospital,

2 cases of appendicitis, 1 involving a retrocecal appendix and 1 a ruptured appendix with free air under the diaphragm, were diagnosed preoperatively as cases of perforated peptic ulcer. The following conditions were encountered in the same period and were diagnosed preoperatively as perforated peptic ulcers: an internal hernia through the foramen of Winslow, with gangrenous bowel; massive gangrene of the small bowel, due to sclerosis of the terminal arterioles, observed in a Negro 40 years of age; carcinoma of the stomach with perforation; acute cholecystitis with rupture, and diverticulitis of the colon with rupture and free air under the diaphragm. Many of these conditions are rare, but they constitute emergencies which do not benefit by surgical delay.

4. With the nonoperative method, the diagnosis is not absolute because it is not confirmed by operation. The results of this method, especially as expressed in mortality rates, are therefore open to question, because some cases may be included in a series which are not really cases of perforated ulcer. For example, in Taylor's original report only 2 of the 28 patients were described as having free air under the diaphragm. Ten other cases were confirmed by means of subsequent roentgenograms or operative evidence of ulcer. In the remaining 16 cases the diagnosis rested on purely clinical grounds. Seeley has demonstrated free air under the diaphragm in only 50 per cent of his cases. Over the last fifteen years, with repeated analyses of our cases proved by operation, free air under the diaphragm has been consistently demonstrated in 65 per cent. It is our belief that there is no absolute method of making a diagnosis of perforated peptic ulcer in 100 per cent of the patients treated without operation.

5. We have noted that when there is a large perforation, a centimeter or more in diameter, duodenal fluid or regurgitated jejunal or ileal contents may continue to escape into the peritoneal cavity even though gastric suction is adequate to keep the stomach empty. Large perforations do not tend to close spontaneously. Three examples of this fact were seen recently. A recluse was brought to the Cincinnati General Hospital in profound shock, with evidence of perforated ulcer. He was given a blood transfusion, and suction was started, but his condition did not improve until twenty-four hours had elapsed. Twenty-nine hours after his admission there was marked evidence of shifting dulness in the abdominal cavity in spite of the large Levin tube in his stomach. Because of the free abdominal fluid, a stab wound was done with the use of local anesthesia without removing the patient from his bed. Two thousand cubic centimeters of bile-stained fluid was obtained. The patient's condition improved, and copious amounts of the same material drained for three days. On the third day the fluid became

blood tinged, and later clotted blood appeared. The patient died on this day. Autopsy revealed a 1 cm. hole on the anterior surface of the duodenum, whence bile and blood continued to drain in spite of the fact that his stomach was empty. The second example was a 60 year old man who was operated on sixteen hours after perforation. There were minimal abdominal findings, but at operation there was a hole 8 mm. in diameter through which duodenal contents were pouring in spite of the presence of a large Levin tube and the fact that the stomach was empty. Recovery was uneventful. The third case was that of the 40 year old Negro previously described, with far advanced tuberculosis, who had an anterior duodenal perforation closed. He died from leakage of a second perforation five days later, in spite of aspiration and chemotherapy.

Since the advent of the routine use of penicillin in the operative treatment of perforated peptic ulcer, wound infections, which previously complicated 10 to 20 per cent of the cases, have disappeared. Before the use of chemotherapy and antibiotic therapy, the incidence of wound infection was 20 per cent. With the use of the sulfonamide drugs, the rate dropped to 10 per cent, and with the addition of penicillin wound infection has ceased to occur. No subphrenic abscesses have been seen following the closure of perforated ulcers in the group of patients treated with penicillin at the Cincinnati General Hospital. One such abscess was seen in a case in which a perforation had been closed at another hospital, the patient having received penicillin for only four days.

Wound disruption occurred in a cirrhotic patient whose wound was closed with through and through steel wires. There has been a recent disruption in a patient whose wound was closed with buried steel wires. This patient became delirious prior to the wound disruption but survived. Our previous incidence of wound disruption was 2.7 per cent.

We believe that the nonoperative method of treatment should be reserved for poor risk patients and for those in areas in which surgical service is not available. It should certainly be instituted early with patients in whom perforated peptic ulcer is suspected and/or cannot be ruled out.

The diagnosis of perforated peptic ulcer continues to be missed, and in spite of all the advances in chemotherapy the mortality rate in patients who are not treated before twenty-four hours have elapsed remains over 60 per cent. We have noted in our own hospital that perforations occurring in patients in allied services are seldom closed before twelve hours. This type of patient would certainly benefit by immediate gastric suction and chemotherapy when the diagnosis is first suspected.

The considerable reduction in the mortality rate in cases of acute peptic ulcers seen early (in the last five years we have had no deaths

in patients operated on within six hours of perforation) has encouraged us to consider gastric resection for certain selected cases. This method has been popular in Europe, and according to a recent report from Italy by Manzocchi [4a] 22 of 65 patients were treated with resection, with a mortality of 4 per cent. Bisgard [5] has indicated that, in competent hands, perforations observed early in patients in good condition can be treated by means of resection, with no higher mortality than that from simple closure of the ulcer. Simple closure is only a temporary method of treatment in many cases. Illingworth [6] reported 880 cases of perforated ulcers which were closed, with relapse of symptoms in 40 per cent of the cases. In 20 per cent of the cases there were serious complications such as hemorrhage or reperforation. We find it difficult to convince the type of patient with which we are dealing that an operation to cure the ulcer is necessary after recovery from the acute perforation. In addition, many of these persons are unable to follow any kind of dietary regimen because of insufficient funds. At the Cincinnati General Hospital there has been a reperforation rate of 10 per cent in the last 128 cases and of 20 per cent in the last year. Freedom from symptoms following the closure of a perforated ulcer does not mean that reperforation might not occur.

In the last year 3 patients who had reperforation were treated by gastric resection. Their postoperative courses were not unlike those of patients who had undergone simple closure of the ulcer. To date, gastric resection has been used only in cases of reperforation, when the patients have been seen early and have been in good condition. This procedure could be safely extended to patients who give a long history of ulcer, with complications such as hemorrhage and obstruction, and to persons who have perforated gastric ulcers. Gastric resection should be considered in cases of perforated peptic ulcers associated with hemorrhage. Unfortunately, it is often difficult to be sure of the diagnosis of associated bleeding. It should be considered seriously in cases in which the shock or the shocklike syndrome does not respond to simple intravenous administration of fluids. Two such cases in this series were not recognized until necropsy was performed. It should be stressed that the patient must be in good condition and that the duodenum should be relatively free posteriorly, so that duodenal closure can be done easily. The majority of free perforations occur in the anterior portion, leaving the posterior segment of the duodenum clear. If gastric resection is to be

4a. Manzocchi, L.: Considerazioni su 941 interventi per perforazione gastroduodenale, Chirurgia **3**:105, 1948; Internat. Abstr. Surg. **88**:505, 1949; in Surg., Gynec. & Obst. June 1949.

5. Bisgard, J. D.: Gastric Resection for Certain Acute Perforated Lesions of the Stomach and Duodenum with Diffuse Soiling of the Peritoneal Cavity, Surgery **17**:498-509, 1945.

6. Illingworth, C. F. W.; Scott, L. D. W., and Jamieson, R. A.: Progress After Perforated Peptic Ulcer, Brit. M. J. **1**:787-790, 1946.

considered, it is of paramount importance that the diagnosis be made quickly and that chemotherapy be started at once. If gastric resection is to be done for perforation, it should be done within a reasonable length of time.

The following points are reemphasized with regard to the early diagnosis of acute perforated peptic ulcer, since patients with this condition are not uncommonly seen late. Seventy-five per cent of our patients gave a history of epigastric distress. Between 60 and 70 per cent of the patients had free air under the diaphragn, this percentage depending, to some extent, on how thorough the roentgenologic studies were. At least 10 per cent of our patients had the symptoms and signs of appendicitis. Abdominal findings are often variable, changing from hour to hour and giving the temporary observer a false impression. We have found the respiratory rate in cases of acute perforation to be consistently increased. At operation the diagnosis of the site of free perforation is sometimes difficult, in spite of a large amount of soiling. In cases of tiny posterior perforations, methylene blue instilled in the stomach will shorten the operation time by helping the surgeon to find the perforation. A posterior gastric perforation may have no palpable induration.

SUMMARY AND CONCLUSIONS

1. The mortality rate at the Cincinnati General Hospital among patients in whom perforated ulcers were closed up to twenty-four hours after perforation (122 cases during the last five years) was 4 per cent.

2. If one excludes the deaths from causes not attributable solely to the perforation the mortality rate drops to less than 1 per cent. This mortality rate should be attained by the use of the operative method in good risk patients.

3. Vigilance must be maintained for the early diagnosis of the bizarre and atypical cases of perforation of peptic ulcer, often missed in the early stages of this condition.

4. The nonoperative method of treatment is still unproved, and until more patients have been treated with this method its value is questionable. Only definite cases of perforated ulcer should be included in determining mortality rates, and with the nonoperative method it is difficult to verify all cases. Responsibility must be assumed for deaths occurring from other surgical emergencies when these are misdiagnosed as acute perforation of ulcer and treated by nonoperative methods.

5. With the present low operative mortality in cases of perforated peptic ulcer, gastric resection, rather than simple closure, should be considered for certain patients in good condition who are seen early. These should include patients with reperforation, gastric ulcers possibly due to carcinoma, a chronic history of obstruction or hemorrhage and perforations associated with hemorrhage.

MASSIVE HEMORRHAGE FROM THE UPPER GASTROINTESTINAL TRACT

A Study of Three Hundred and Twenty-Four Cases Observed at the Detroit Receiving Hospital Over a Nine Year Period

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DETROIT

THE PURPOSE of the paper is (1) to report on the causes of massive hemorrhage from the upper gastrointestinal tract, (2) to outline methods of diagnostic procedure when confronted with such bleeding, (3) to discuss nonoperative management of bleeding peptic ulcer and factors effecting mortality of this condition, (4) to contrast the results of conservative and surgical treatment and (5) to outline the indications for surgical intervention in bleeding ulcer and discuss operations performed. Our conclusions are based on a study of all available patients and records in the City of Detroit Receiving Hospital from 1940 through 1948 in which the presenting symptom on admission was bleeding from the upper gastrointestinal tract.

CAUSES OF MASSIVE HEMORRHAGE IN OUR SERIES

Table 1 presents the causes for massive hemorrhage in our series. Peptic ulcer is the most frequent cause of massive hemorrhage and accounted for 76 per cent of cases. A positive diagnosis of ulcer was established by roentgen examination, operation or autopsy in the 147 cases of duodenal ulcer, 45 cases of gastric ulcer and 8 cases of marginal ulcer.

The 46 cases of probable peptic ulcer referred to in table 1 involved patients for whom we had no opportunity to confirm the diagnosis in our own x-ray department. In most cases the patients gave a history of ulcer and their roentgenograms were said to reveal the presence of ulcer.

Bleeding of undetermined origin was diagnosed when there were no definite findings to account for the bleeding. Roentgenograms were taken of many of the patients, with negative results, and a few were operated on with no cause of the hemorrhage being evident.

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DIAGNOSTIC PROCEDURES

1. A history is elicited and physical examination carried out in an attempt to determine the cause of the bleeding. The character of the vomitus and stools should be recorded.

2. Clinical estimation is made of the severity of the bleeding. The general appearance of the patient, pulse rate, blood pressure, pallor of skin and mucosae, history of fainting and presence of shock are important. We have classified the severity of bleeding on the basis of I through IV, depending on the criteria given in table 2. Rigid standards are not

TABLE 1.—*Cause of Massive Hemorrhage from Upper Gastrointestinal Tract in 324 Patients*

			Total
1.	Duodenal ulcer	147	
2.	Gastric ulcer	45	
3.	Marginal ulcer	8	
4.	Probable peptic ulcer	46	
	Total patients with ulcer		246
5.	Carcinoma of stomach		6
6.	Esophageal varices (cirrhosis)		34
7.	Bleeding of undetermined origin		26
8.	Bleeding with partial thoracic stomach		4
9.	Miscellaneous causes (1 each)		8
	Gastric plus duodenal ulcer; bleeding perforated duodenal ulcer; schwannoma; ectopic pancreatic tissue in stomach; hemorrhagic gastritis; hepatoma with cirrhosis; prolapsed gastric mucosa; sarcoma of stomach		
			324

TABLE 2.—*Bleeding Peptic Ulcer; Severity of Bleeding Classification*

Class I	Mildly severe bleeding. No obvious shock. Blood pressure and pulse within normal limits.
Class II	Moderately severe bleeding. Only mild shock, although there is evidence of considerable blood loss.
Class III	Severe bleeding. Obvious clearcut evidence of sustained shock with the systolic blood pressure below 80 mm. and a markedly increased pulse rate.
Class IV	Exsanguinating hemorrhage. The patient presents a picture of impending death. Systolic blood pressure from 70 mm. to 0 and pulse often unobtainable.

set; the figures are approximations, but we have found the classification extremely useful. This classification of hemorrhage is based on the data obtained when the patients were admitted to the hospital.

3. Since we have no facilities for rapid studies of blood volume, determination of hemoglobin, red blood cell count and hematocrit value are done in spite of the fact that they give only a rough and frequently erroneous estimation of the amount of blood loss. The results are not relied on too closely but are used as supporting data along with clinical findings.

4. It is at times difficult to differentiate bleeding due to peptic ulcer and that due to esophageal varices. Simple liver function tests may be useful in an acute emergency. Determination of cephalin flocculation, quantitative bilirubin and prothrombin time may be carried out rapidly

and without undue disturbance to the patient. More recently we have found the use of the Patton tube [1] valuable in differentiating these two conditions.

5. Rarely bleeding from the upper gastrointestinal tract results from blood dyscrasia, but in such instances the diagnosis can usually be made from the history and the physical examination. Obviously when such disease is suspected thorough hematologic studies are indicated. No cases of the condition were encountered in this series.

6. The early use of roentgenologic examination in the presence of bleeding will add valuable information and guidance in the management of patients with peptic ulcer, and we have no hesitancy in using the x-ray when the question of surgical intervention presents itself. Schatzki [2] early pointed out that there had been unnecessary conservatism in the use of roentgen examinations during bleeding.

BLEEDING PEPTIC ULCER

Nonoperative Management.—1. All patients on their entrance to the hospital should have blood drawn for typing and cross matching. Patients with severe hemorrhage should be given transfusions immediately. Many transfusions may be necessary and occasionally through more than one port, and at times arterial transfusion may be needed.

2. Gastric intubation with suction is important, for it helps to prevent vomiting, allows the administration of thrombin and buffer [3] and gives an index of the amount of bleeding.

3. Sedation with phenobarbital sodium may be of value.

4. Diet is one of the many variables in nonoperative treatment such as age of the patient, severity of hemorrhage, number of previous hemorrhages and amount of blood lost, and it is therefore difficult to draw conclusions as to the efficacy of a particular diet. It is wrong to think of a diet as a method of stopping bleeding. Either the patient has a mild hemorrhage and can be fed or he has a severe hemorrhage and means for stopping the blood loss become paramount. Meulengracht's [4] great contribution to the treatment of bleeding ulcer consisted in the administration of a high protein diet, augmented by iron, which accelerated blood regeneration and shortened convalescence. The use of the Meulengracht diet at Receiving Hospital was reported by Mayer and

1. Patton, Thomas B., and Johnston, Charles G.: A Method for Control of Bleeding from Esophageal Varices, Arch. Surg. **59**:502-506 (Sept.) 1949.

2. Schatzki, R.: Roentgenologic Examination in Patients with Bleeding from Gastrointestinal Tract, New Eng. J. Med. **235**:783-786 (Nov. 28) 1946.

3. Daly, B. M.: The Management of Patients with Bleeding from the Upper Gastrointestinal Tract with Buffer and Thrombin Solution, Ann. Surg. **129**:832-839 (June) 1949.

4. Meulengracht, E.: Treatment of Hæmatemesis and Melæna with Food: Mortality, Lancet **2**:1220-1222 (Nov. 30) 1935.

Lightbody[5] in 1939 and 1941. They were unable to equal Meulengracht's mortality of 1.3 per cent for medically treated patients, their mortality being 3.8 per cent if all deaths were included. In our series of medically treated patients with bleeding peptic ulcer there were 25 deaths in 201 patients, a mortality of 12.4 per cent. The mortality of bleeding peptic ulcer depends on the mildness or severity of the hemorrhage. There has been a marked variation in the mortality reported from bleeding peptic ulcer treated medically, varying from 1.3 per cent reported by Meulengracht to 25 per cent reported by Chiesman.[6] Many large series of cases have been reported with a medical mortality of between 10 and 15 per cent.[7] Our mortality of 12.4 per cent is in accord with this group. The patients whom we have seen in private practice have a low mortality rate as they comprise a group in whom bleeding is mild or moderate. Severe and exsanguinating hemorrhage is much commoner in large city hospitals with emergency ambulance services than in private hospitals. We have seen many patients rushed directly to our hospital by ambulance without having been examined by a physician.

Factors Effecting Mortality.—1. Age: Bleeding occurred at all ages from 20 to 80 years. About one third of the patients who bled severely (classes III and IV) were under the age of 40. It has been repeatedly pointed out that age is a most important factor in the prognosis of hemorrhage due to peptic ulcer. Chart 1 gives a breakdown of the mortality rate of peptic ulcer as related to age; as one would expect, the rate is highest in the older age group, but it is well to point out that younger patients can bleed to death from peptic ulcer.

2. Location of Ulcer: In the group of patients not operated on there were 117 with duodenal ulcer, of whom 11 died, a mortality of 9.4 per cent, and 32 with gastric ulcer, of whom 8 died, a mortality of 25 per cent. The mortality from bleeding gastric ulcer is thus much higher than that from bleeding duodenal ulcer. Our results are in agreement with those of Welch and Yunich,[8] who found a 35 per cent mortality

5. Mayer, Willard D., and Lightbody, James J.: Further Observations on the Use of Food in the Treatment of Bleeding Peptic Ulcer, Rev. Gastroenterol. **8**:1-5, 1941.

6. Chiesman, W. E.: Mortality of Severe Hemorrhage from Peptic Ulcer, Lancet **223**:722-723 (Oct. 1) 1932.

7. Aitken, R. S.: The Treatment of Profuse Bleeding from the Stomach and Duodenum, Lancet **1**:839-842 (April 21) 1934. Allen, Arthur W., and Benedict, Edward B.: Acute Massive Hemorrhage from Duodenal Ulcer, Ann. Surg. **98**:736-749, 1933. Hellier, F. F.: Aetiology and Mortality Rate of Haematemesis, Lancet **2**:1271-1274 (Dec. 8) 1934. Holman, Cranston W.: Further Observations on the Treatment of Bleeding Peptic Ulcer, Surgery **23**:405-409 (March) 1948. Bulmer, Ernest: Mortality from Hæmatemesis, Lancet **2**:720-722 (Oct. 1) 1932.

8. Welch, C. S., and Yunich, A. M.: The Problem for Surgery in the Treatment of Massive Hemorrhage of Ulcer Origin, Surg., Gynec. & Obst. **70**:662-665, 1940.

for bleeding gastric ulcer as contrasted with a 6 per cent mortality for bleeding duodenal ulcer. Therefore one would be more apt to advise gastric resection for bleeding gastric ulcer than for duodenal ulcer.

3. Number of Hemorrhages: Table 3 shows the mortality among patients with proved duodenal ulcer as related to the number of times the patient has bled. There is an appreciable incidence of deaths with the first hemorrhage. The statement has often been made that patients with multiple hemorrhages should be more seriously considered for operation than patients with an initial hemorrhage. Our figures show

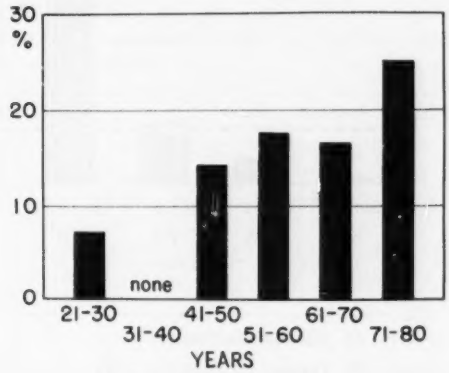

Chart 1.—Age of patients.

TABLE 3.—*Number of Hemorrhages; Duodenal Ulcer*

	Total Cases	Death	Mortality, %
One hemorrhage	100	16	16
Two hemorrhages	35	0	0
Three or more hemorrhages	12	3	25

this to be true for the group who have bled three or more times, but we had no deaths in the group admitted for the second hemorrhage, and if these two groups are considered together the fatality rate for multiple hemorrhage is less than that for the initial hemorrhage.

4. Severity of Hemorrhage: We believe that the most important factor in mortality of bleeding peptic ulcer is the severity of hemorrhage. Chart 2 shows the mortality of peptic ulcer as related to the amount of blood loss. It can be seen that there is an appreciable number of deaths among patients admitted with mildly severe symptoms and little blood loss since the bleeding may later become severe and with increasing severity of hemorrhage the mortality rises. Chart 3 compares the mortality of patients with bleeding peptic ulcer treated medically and those treated by gastric resection. It is apparent that patients with

exsanguinating hemorrhage have a high fatality rate when treated medically. When the natural cause of the disease is interrupted by gastric resection, there is no longer a direct relation between severity of hemorrhage and end results. With increasing experience in selecting cases for operation and increasing skill in surgical management, a lower

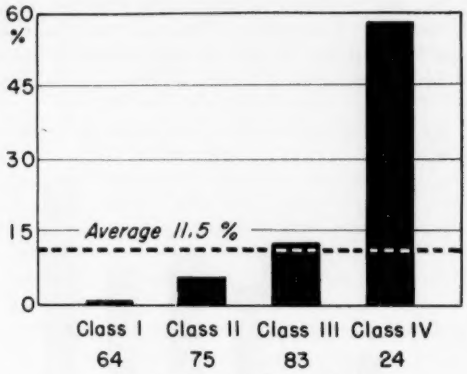

Chart 2.—Severity of hemorrhage.

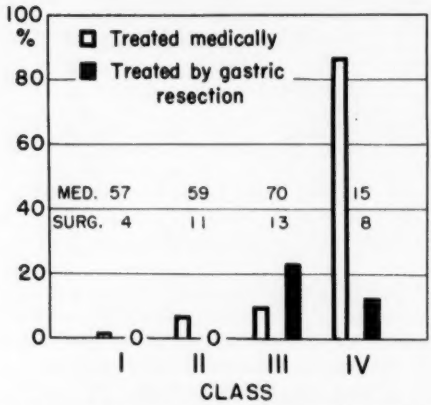

Chart 3.—Comparison of surgical and medical mortality.

fatality rate will be obtainable. During the period of time covered for this study, most of the patients were admitted to the medical service and the ones with severe bleeding were referred for surgical treatment after all means of stopping the hemorrhage by nonsurgical methods had failed. There can be no doubt that the results would have been better had the cases for operation been selected earlier.

Indications for Surgical Treatment.—1. All patients with exsanguinating hemorrhage resulting in severe sustained shock (class IV) and patients with moderate depression of blood pressure who do not respond to vigorous blood replacement should be operated on without delay. If the blood pressure cannot be maintained, it usually means that bleeding is continuing and hemostasis must be obtained by surgical means.

2. In all cases bleeding gastric ulcer should be resected without delay. The mortality for this condition is three times that for duodenal ulcer, and one cannot exclude the possibility of carcinoma.

3. Patients with hemorrhage which stops and starts again should be operated on, for these do poorly with conservative management, particularly when continued unsuccessfully for a long time, and then late operation becomes hazardous.

4. Two or more previous hemorrhages should be an indication for resection. It seems reasonable to subject these persons to gastric resection rather than to risk their lives repeatedly with subsequent hemorrhage.

5. Patients with massive hemorrhage in addition to a complication of peptic ulcer which is generally considered to make surgical intervention justifiable within itself require urgent surgical treatment. Such complications are pyloric obstruction, perforation and lack of response to adequate medical therapy.

OPERATIONS PERFORMED

Fifty-nine operations were performed in a total of 324 patients with massive hemorrhage, an incidence of 18 per cent. A number of interesting conditions were encountered such as gastric resection for bleeding ectopic pancreatic tissue, schwannoma (neurilemoma), sarcoma of stomach and prolapse of gastric mucosa through the pylorus.

There were six gastric resections for carcinoma of the stomach with massive hemorrhage. There were no operative deaths in this group.

The operation of choice in massive bleeding from peptic ulcer is gastric resection. This operation was performed in 36 of the 246 patients with peptic ulcer. There were 4 deaths among the 36 patients, a mortality of 11.1 per cent. The mortality for resection for gastric ulcer was 7.6 per cent, which is considerably less than the mortality for duodenal ulcer (13.3 per cent). This fact, coupled with the greatly increased mortality from medical treatment of bleeding gastric ulcer, constitutes an excellent reason for performing resection on all patients with bleeding gastric ulcer.

EMERGENCY VERSUS INTERVAL OPERATION

Gastric resection is performed in one of three sets of circumstances.

A. *Emergency Procedure in Patients with Class IV Bleeding.*—This is the group which carries an 86 per cent mortality with conservative

management, and the mortality will be higher than that in patients on whom elective procedures are performed because of the presence of uncontrolled hemorrhage and blood deficit. However, many patients with exsanguinating hemorrhage can be salvaged by gastric resection, with liberal use of blood before and during the operative procedure. In choosing patients for emergency operation, the crucial point is the rate of bleeding. When bleeding continues at a rapid rate despite heroic efforts to replace blood, the risk of medical treatment is greater than the risk of operation.

B. *Delayed Emergency Surgical Procedure.*—After the hemorrhage has subsided and the hemoglobin is brought up to satisfactory levels by transfusion, gastric resection is performed. In this group of patients the risk of operation is not great and closely approximates that of elective surgical procedures. These patients are operated on usually toward the end of the first week after their admission to the hospital for bleeding.

C. *Elective Operation.*—The patient has completely recovered from the hemorrhage and may have been discharged from the hospital and brought back in to be operated on. The mortality in this group should be low, approximating that for nonbleeding ulcer.

In our series there were 36 patients who underwent gastric resection for peptic ulcer. Of this group, 11 had emergency resection for exsanguinating hemorrhage, with 2 deaths, giving a mortality of 18 per cent. Nineteen patients underwent delayed emergency operations, with 1 death, a mortality of 5 per cent. Six patients were subjected to interval operations after the bleeding had stopped. The number of interval operations reported in this series is small because we have included only those patients admitted to the hospital for massive bleeding.

SUMMARY AND CONCLUSIONS

1. Seventy-six per cent of all patients with massive gastrointestinal hemorrhage had peptic ulcer.

2. The most essential nonoperative factor in handling patients with massive bleeding is adequate blood replacement.

3. Factors effecting mortality in bleeding peptic ulcer are age of the patient, location of the ulcer, number of hemorrhages and severity of the hemorrhage.

4. The indications for surgical intervention have been outlined.

5. In tabulating end results, it can be shown that there is a direct relation between severity of hemorrhage and mortality.

6. The use of liberal amounts of blood and proper selection of patients for operation make gastric resection a safer procedure in certain cases of bleeding peptic ulcer than watchful waiting, which was formerly the rule.

QUESTION OF THE RETURN OF GASTRIC SECRETION AFTER COMPLETE VAGOTOMY

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THE QUESTION of regeneration of the vagus nerves and return of gastric secretion after complete vagotomy has become of great clinical as well as scientific interest because of the widespread use of section of the vagus nerves as a method of treatment of various types of peptic ulcer in man. It seems highly probable that the beneficial effects of this operation are largely due to the marked reduction in the secretion of gastric juice both in the fasting stomach and as a result of the stimulation of food. Perhaps to a lesser extent some of the beneficial effects of vagotomy may be ascribed to a decrease in the hypertonicity and hypermotility of the stomach so frequently found in patients with duodenal ulcers. Accordingly, if vagotomy is to be of long-continued or permanent value in the treatment of peptic ulcer, the effects on secretion and motility ought to be long continued or permanent. It is perhaps surprising that regeneration of the vagus nerves following section seems not to have been extensively studied, nor have many long term studies been made of the effect of vagotomy on gastric secretion and motility. In 1929 Hartzell [1] studied the effect of transthoracic vagotomy on four dogs by means of fractional analyses of the concentration of free and total hydrochloric acid in the stomach after the administration of a standard test meal of ground, lean horse meat. A considerable reduction in both the free and the total acidity of the gastric content was found which persisted for the period of observation, one to five months.

From the Department of Surgery of the University of Chicago.

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This work has been aided by grants from the Otho S. A. Sprague Memorial Institute and from the Division of Research Grants and Fellowships of the National Institutes of Health, United States Public Health Service.

1. Hartzell, J. B.: The Effect of Section of the Vagus Nerves on Gastric Acidity, Am. J. Physiol. **91**:161, 1929.

Two and one-half years after operation Vanzant[2] studied the gastric secretion in three of the dogs on which Hartzell had performed a transthoracic vagotomy and, utilizing Hartzell's method of fractional analysis, reported that by this time the acidity of the gastric content had returned to approximately the normal level. Moore and his associates[3] have reported that the early decrease in fasting acidity and motility, which is so readily demonstrable after vagotomy, gradually returns toward normal until at the end of a year no abnormality can be found by these criteria. These impressions that the effect of vagotomy on gastric secretion is transitory are not borne out by a rather extensive series of observations made in our clinic and laboratories, the data on which form the basis of this report.

It should be recognized that two distinct problems are involved in these studies: first, the question of regeneration of the divided vagus nerves, and, second, the question of a return of gastric secretion to the state existing before the operation. It is conceivable, of course, that gastric secretion might return to the preoperative state even though regeneration of the vagus nerves had not occurred and be due to the compensatory effect of other factors affecting gastric secretion.

The difficulty of preventing nerve regeneration after sympathectomy was well known, and for this reason regeneration of the divided vagi was anticipated as a possibility when vagotomy was introduced in our clinic in 1943.[4] It was appreciated, however, that damage to the recurrent laryngeal nerve after thyroidectomy is seldom, if ever, followed by regeneration, and in a fairly extensive laboratory experience with isolated small stomach pouches of the Heidenhain type reinnervation of the isolated stomach by vagus fibers never occurred. In the first patients on whom vagotomy was performed by the transthoracic approach, short segments of the nerves were excised, but otherwise the nerve trunks were undisturbed. It was hoped that should untoward results be seen regeneration of the nerve fibers might take place and correct the difficulty. Subsequently, larger segments of the vagus nerves were excised, and in some cases the proximal portions of the nerves were transplanted into the pleural cavity so that regenerating fibers would have difficulty in finding their peripheral connections. With the adoption of the abdominal approach for vagotomy, transplantation

2. Vanzant, F. R.: Late Effects of Section of the Vagus Nerves on Gastric Acidity, Am. J. Physiol. **99**:375, 1932.

3. Moore, F. D.; Chapman, W. P.; Schulz, M. D., and Jones, C. M.: Resection of the Vagus Nerves in Peptic Ulcer: Physiologic Effects and Clinical Results, with a Report of 2 Years' Experience, J. A. M. A. **133**:741 (March 15) 1947.

4. Dragstedt, L. R., and Owens, F. M., Jr.: Supra-Diaphragmatic Section of the Vagus Nerves in Treatment of Duodenal Ulcer, Proc. Soc. Exper. Biol. & Med. **53**:152, 1943.

of the proximal segment was abandoned in favor of resecting 2 to 5 cm. of the nerve trunks between ligatures of nonabsorbable suture material. In all cases a considerable gap between the divided nerve ends resulted.

EXPERIMENTAL DATA

Quantitative studies of gastric secretion can be most accurately carried out on dogs provided with the type of vagally innervated, totally isolated stomach illustrated in the accompanying figure. In a previous report from this laboratory [5] concerning 12 animals with this type of preparation, section of the vagus nerves was found to produce an immediate reduction of 76 per cent in the 24 hour output of hydro-

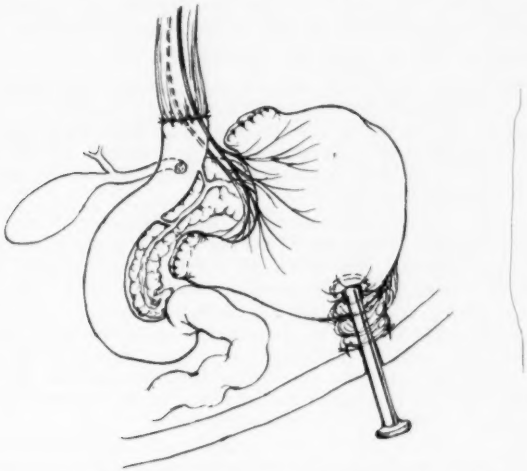

Diagram illustrating the totally isolated stomach, with preservation of the vagus nerve supply (Dragstedt-Ellis pouch). (Woodward, Harper, Tovee and Dragstedt.[5])

chloric acid. Reactions to insulin tests, which had been positive before vagotomy, were all negative subsequently. Four of the animals survived for periods varying between four and six months, and during this time the insulin reactions remained negative and the gastric secretion remained at the low level. Animal D-962 is of especial interest, since it is still living two years subsequent to the vagotomy, and we have records of 750 separate 24 hour collections of gastric secretion.

5. Woodward, E. R.; Harper, P. V., Jr.; Tovee, E. B., and Dragstedt, L. R.: Effect of Vagotomy on Gastric Secretion in Man and Experimental Animals, Arch. Surg. **59**:1191 (Dec.) 1949.

Before vagotomy, the isolated stomach of this animal put out 44.1 milliequivalents of hydrochloric acid in 24 hours, this being the average of 87 twenty-four hour collections. After vagotomy, the output of hydrochloric acid decreased to 8.3 milliequivalents. Two years later the reaction to the insulin test was still negative, and the hydrochloric acid output averaged 11.3 milliequivalents in a 24 hour period. It should be emphasized that in this animal the vagus nerves in the chest were crushed with a heavy clamp but not divided. In spite of the resulting anatomic continuity which should provide an optimum opportunity for regeneration, this did not occur, as evidenced both by the insulin test and by the continued reduction in gastric secretion.

The problem of regeneration of the vagus nerves after crushing in the chest has also been studied in two animals provided with a simple gastric fistula and in four with Pavlov pouch preparations. The data are summarized in the following protocols:

Dog D-950.—On Jan. 24, 1947, both vagus nerves were secured immediately above the diaphragm by a transthoracic operation and crushed with a heavy Kocher forceps. On November 13 a cannula gastrostomy was made to simplify the collection of gastric juice. During the period from December 1947 to January 1950, eleven insulin tests with adequate degrees of hypoglycemia were performed, and all gave negative reactions.

Dog D-913.—A cannula gastrostomy was performed on June 11, 1947. Two insulin tests gave strongly positive reactions. On June 24 the vagi were divided above the diaphragm. Nine insulin tests performed during the period between June 1947 and January 1950 elicited negative reactions.

Dog D-879.—On Feb. 7, 1947, a large Pavlov pouch was constructed. During the first two months after the operation, five insulin tests gave negative results. However, on April 24 and 30 reactions to insulin tests were strongly positive. On July 10 the vagus nerves were crushed above the diaphragm, and subsequently eight insulin tests performed in the period between the operation and the animal's death on Sept. 14, 1949; all gave negative reactions.

Dog D-928.—On Sept. 8, 1947, a large Pavlov pouch was constructed. An insulin test on September 27 gave a negative reaction, but one on October 18 gave a strongly positive response. Two additional tests on November 19 and on Jan. 14, 1948, also elicited strongly positive reactions. On Jan. 15, 1948, the vagus nerves were crushed in the chest above the diaphragm. During the subsequent two years to January 1950, five insulin tests were performed and all gave negative reactions.

Dog D-944.—On Nov. 28, 1947, a large Pavlov pouch was constructed. Reactions to insulin tests on November 19 and on Jan. 14, 1948, were positive. On Feb. 3, 1948, the vagi were crushed in the chest just above the diaphragm. On June 28, 1948, an insulin test was performed and the reaction found negative.

Dog D-949.—On Nov. 11, 1947, a large Pavlov pouch was constructed. An insulin reaction on December 3 was interpreted as probably positive. On Jan. 28, 1948, the reaction was definitely positive and on May 12 strongly positive. On May 14, 1948, the vagi were crushed in the chest above the diaphragm. Three insulin tests performed in the period between the operation and the animal's death on Feb. 4, 1949, gave entirely negative reactions.

CLINICAL OBSERVATIONS

The observations that we have made on patients with duodenal ulcer subjected to vagotomy in general confirm the more exact studies on experimental animals. The results obtained in 19 of the early patients for whom follow-up studies after intervals of two to seven years were adequate are summarized in the table. When vagotomy was first employed in our clinic in January 1943, the value of the insulin test in determining the completeness of the operation was not appreciated and for this reason preoperative and postoperative tests were not made

Fasting Gastric Secretion in Patients with Duodenal Ulcer Before and After Vagotomy

	Preoperative Period				Postoperative Period					Follow-Up Data			
	Night Secretion				Night Secretion					Night Secretion			
Patient	Volume, Cc.	Free Acid, Clinical Units	Acid Output, M Eq.	Insulin Test	Volume, Cc.	Free Acid, Clinical Units	Acid Output, M Eq.	Insulin Test	Years Since Vagotomy	Volume, Cc.	Free Acid, Clinical Units	Acid Output, M Eq.	Insulin Test
1	1,160	65	75.4	..	310	58	18	..	4¼	630	0	0	—
2	1,450	70	101.5	..	510	56	29	..	7	710	22	15.6	—
4	780	51	39.7	..	250	11	2.7	..	1	535	48	25.6	+
6	1,715	25	42.8	..	688	36	24.7	..	5	410	28	11.5	+
8	930	85	79.0	..	198	21	4.1	..	6	380	18	6.8	—
9	1,150	74	84.0	..	895	60	54.0	..	2¼	372	26	9.6	—
10	800	48	38.4	..	448	22	9.8	..	2	220	52	11.4	—
12	1,855	41	84.0	..	425	21	8.9	..	2	600	54	32.4	+
27	1,130	43	48.6	..	580	0	0	—	5	190	0	0	—
28	1,400	91	127.0	+	800	81	64.8	—	2	710	61	43.3	—
36	680	75	51.0	+	225	7	1.5	—	4	840	16	13.0	—
7	1,650	43	71.0	..	690	5	4.0	..	1½	270	32	9.0	..
11	2,000	34	68.0	..	530	30	16.0	..	4	834	23	19.0	..
100	1,500	67	100.0	+	...	..	....	..	3	1,000	27	27.0	..
71	950	55	52.0	+	520	0	0	—	3	370	0	0	—
59	960	49	47.0	..	660	46	30.4	..	3½	320	0	0	—
189	590	28	17.0	+	890	7	6.0	..	2	700	0	0	—
231	550	12	7.0	+	2,000	0	0	—	2½	250	0	0	—
178	1,220	40	49.0	+	...	..	....	..	3	640	0	0	—

in the early cases. This procedure is now routine. The continuous secretion of the stomach in the absence of the stimulus of food was examined rather than the response to test meals or histamine. The volume and the free acidity of the gastric content, aspirated by means of an intranasal gastric tube and continuous suction, were recorded. The product of the volume in liters and the free acidity expressed in clinical units represent the total hydrochloric acid output in milliequivalents during the 12 hour period of collection. This is of course a minimum figure, since some gastric juice escapes through the pylorus and some acid is neutralized by swallowed saliva and gastric mucus. When gastroenterostomy is added to vagotomy, acid neutralization by duodenal content may be considerable, and for this reason only patients treated by vagotomy alone were selected for this study. Our first two patients

are perhaps the most interesting because for these we have the longest follow-up and because, as noted above, no precautions were taken to prevent vagus nerve regeneration. These men put out an average of 75.4 and 101.5 milliequivalents of hydrochloric acid in the fasting night secretion before vagotomy, which contrasts markedly with the 18 milliequivalents secreted by normal persons. This hypersecretion was reduced by the operation to 18 and 29 milliequivalents respectively. When the first man was checked four years and three months after the vagotomy, no free acid was found in his night secretion on repeated testing, and there was no secretory response to insulin hypoglycemia. In the second patient, tested after seven years, the output of hydrochloric acid had decreased still further to 15.6 milliequivalents and the insulin reaction was likewise negative. Three of the patients in this series (4, 6 and 12) were found to have positive reactions to insulin tests when examined after one, five and two years respectively. While in each instance the night secretion was less than before vagotomy, the reduction was only 58 per cent as compared with an average of 87 per cent in the remaining patients whose reactions to insulin tests were persistently negative.

COMMENT

The data obtained in our experimental laboratories and in the clinic are thus in agreement and indicate that after complete vagotomy the nervous or cephalic phase of gastric secretion is abolished and that a return of secretion to prevagotomy levels or regeneration of the divided vagi does not occur in periods ranging from two to seven years. The nervous phase of secretion was tested by the gastric secretory response to insulin hypoglycemia, supplemented in a majority of cases by the sham meal. The continuous secretion in the fasting stomach was examined rather than the response to test meals or histamine, because it was the conviction of one of us (L. R. D.) when this work was undertaken that a hypersecretion of gastric juice in the complete absence of the usual physiologic stimulus of food was the most significant alteration in gastric function in patients with duodenal ulcer and one that could be measured with some quantitative precision. Studies of this secretion by the method of fractional analysis are so inadequate as to be almost worthless. In a study of 81 normal persons or patients without gastrointestinal or systemic disease in our clinic, an average of 551 cc., with a free acidity of 33 clinical units, was aspirated from the fasting stomach in a 12 hour period. With the use of the same method on 135 patients with duodenal ulcers, the average volume of night secretion was 1,085 cc. with a free acidity of 52 clinical units. If one were to compare these findings on the basis of the concentration of hydrochloric acid in fractional samples, the conclusion would be reached that the patients with ulcers secreted only 57 per cent more gastric

juice than the normal persons. When, however, the volume as well as the concentration of acid is taken into account, it is seen that the patients with ulcer secrete almost four times as much hydrochloric acid in the fasting secretion. Recent studies supporting the conception of Pavlov that gastric juice is always secreted at a constant acidity make it imperative to measure both volume and acid concentration in all studies on gastric secretion. When neutralization by duodenal secretions obscures the values for free acidity, estimations may be made of the total chlorides of the gastric content, since these are chiefly provided by the hydrochloric acid of the fundus secretion and only in small amounts by the bile and pancreatic juice. It is probable that the discrepancy between our findings and those of Vanzant [2] are due to the fact that she based her conclusions on the acid concentration of fractional samples without data concerning the volume of secretion.

In a recent study from Moore's laboratory,[6] the significance of measurements of the chloride output rate of the stomach is pointed out. Patients with ulcer were found to put out more chloride in a given period than did normal persons, and after vagotomy this output became low and remained low for at least six months. These findings, which are in agreement with those reported in this study, contradict the earlier conclusion of Moore and his associates [3] referred to previously and suggest that this earlier view may have been due to observations made with the method of fractional analysis.

The failure of regeneration of the gastric secretory fibers in the vagus nerves in this series of patients after intervals of two to seven years is significant. When considered in the light of the animal studies, in which interruption of secretory impulses for as long as two years was produced by simply crushing the vagus trunks, they are well nigh conclusive. More animals are, however, being studied and for a longer period before the problem can be considered settled. At present the evidence is strong that after division the vagus nerves do not regenerate. Instances in which, after vagotomy, negative reactions to insulin tests for a time have been followed by positive responses should be interpreted as recovery of traumatized rather than divided nerve fibers.

SUMMARY AND CONCLUSIONS

1. In four dogs with vagally innervated total stomach pouches in which the entire gastric secretion was collected quantitatively vagotomy produced a decrease of 76 per cent in the output of hydrochloric acid, and this persisted for four to six months.

6. Brooks, J. R.; Erskine, J. M.; Gephart, T.; Swain, O., and Moore, F. D.: The Chloride Output Rate of the Human Stomach in Healthy Subjects and Ulcer Patients: The Effects of Vagotomy and Acetylcholine; Studies by the Dye Dilution Technique, Surg., Gynec. & Obst. **90**:155, 1950.

2. In one dog with a vagally innervated total stomach pouch crushing the vagi decreased the hydrochloric acid output from 44.1 to 8.3 milliequivalents in 24 hours and two years later the hydrochloric acid output was still at the low level (11.3 milliequivalents) and the reaction to the insulin test negative.

3. Crushing the vagus nerves in the chest abolished the gastric secretory response to insulin hypoglycemia in four dogs with Pavlov pouches and in one animal with a gastric fistula. No return of vagus function was found when these animals were examined after periods ranging from four months to three years.

4. In 19 patients with duodenal ulcers treated by vagotomy alone the night secretion of gastric juice was markedly decreased and persisted at the low level for periods ranging from two to seven years. In 13 patients a negative gastric secretory response to insulin hypoglycemia was found two to seven years after vagotomy.

5. The failure of Hartzell and Vanzant to note the persistent effect of vagotomy on gastric secretion is probably due to the inadequate testing method employed.

DISCUSSION

ON PAPERS BY HEDIN AND OTHERS; MC ELHINNEY AND ZINNINGER; BROWN AND OTHERS, AND DRAGSTEDT AND OTHERS

DR. CLAUDE J. HUNT, Kansas City, Mo.: I wish to confine my remarks to the papers relative to perforation and to massive hemorrhage. We have not been sympathetic with the medical management of perforation of duodenal ulcer. We have gone on the basis that when a hole was in a viscus it was better to close the hole and then introduce antibactericidal drugs to their maximum effect.

Likewise, we have not practiced resection at the time of closure of a perforation, because we have considered closure of a perforation a lifesaving measure. The object was to close the perforation as soon as possible. These patients are not in suitable condition for surgery, and they are not prepared for such a major operation as gastric resection. However, there is a tendency now to do resections at the time of perforation, especially if the lesion is gastric.

A number of years ago Dr. Bisgard presented before the Western Surgical Association an interesting series of cases in which, at the time of perforation, he had done subtotal gastric resection with success. After that we performed it in one case, and that involved a young man 24 years of age who had previously had three perforations of a duodenal ulcer. We did a gastric resection at the time of the fourth perforation, without incident. We believe that a perforation of a gastrojejunal ulcer is hard to approach and close and a more major procedure should be carried out, such as excision and closure or resection.

Massive hemorrhage of the upper gastrointestinal tract constitutes one of the major problems from the standpoint of judgment and surgical management. When it was related to duodenal ulcer we have proceeded on the basis that if the patient was advanced in age, with arteriosclerosis, it was better to prepare him with multiple transfusions and do a resection early. We have done that satisfactorily on a number of occasions.

I wish to present four slides representative of patients on whom one would of necessity do an immediate operation.

(Slide) The first is a woman 68 years of age who had a hemorrhage in her home, not having previously had any gastric distress, and recovered from it. She had another massive hemorrhage and was admitted to the hospital in an extreme state of exsanguination.

After the first hemorrhage roentgen study was made, and a lesion was found in the fundus of the stomach. When she was admitted in this extreme condition of exsanguination, it was the opinion of all who saw her that life would not last long and that treatment would not be effective. Having experienced this several times with massive hemorrhage from duodenal ulcer, we started immediately to give her blood transfusions through two portals, and she responded. From noon one day to 8 o'clock the next morning she had eleven transfusions, at which time I carried out an exploration. A movable tumor about the size of a small orange was found in the fundus of the stomach, which proved to be a large, benign leiomyofibroma. The pedicle was wide and sufficiently long that it could be easily clamped and the tumor removed without gastric resection. Recovery was uneventful.

(Slide) This is the case of a man 73 years of age who had an advanced exsanguinating hemorrhage. He was given nine transfusions during an interval of almost twelve hours, and at operation this lesion was found similarly placed in the upper part of the stomach. It likewise was excised, and recovery was uneventful.

(Slide) This is the case of a patient over 50 years of age who had marked hemorrhage and dark stools. A lesion previously located on roentgenograms was found at operation in the upper portion of the jejunum. This likewise was a benign lesion of the upper part of the small intestinal tract.

(Slide) The fourth patient had carcinoma of the jejunum, found at operation six months after a resection for carcinoma of the sigmoid which we had performed. It was assumed, because the patient had cancer of the colon, that this was probably a recurrence from the original lesion.

The patient was passing dark stools, and roentgen examination did not reveal any deformity of the small bowel, except in retrospect. After a review of these gastrointestinal pictures it was determined that a diagnosis of a lesion in the small bowel should have been made. This emphasized the point that a separate cancer may be found elsewhere and that one should not jump to the conclusion that a recurrence of symptoms indicates a recurrence of the original cancer. On exploration, however, no metastasis or extensions were found from the previous carcinoma of the sigmoid, and it was with some difficulty that we found and located the soft lesion in the upper part of the small intestinal tract. This was resected; it was a soft, ingrowing neoplastic lesion, involving the jejunal part of the small bowel. It produced no obvious deformity, was soft and spongy and was found only by running the bowel through the fingers in ribbon fashion.

Dr. Roland F. Mueller, Lincoln, Neb.: In commenting briefly on Dr. Brown's excellent paper, I should like to emphasize the importance of this subject. The mortality of massive hemorrhage from this source is high, and we should do everything possible to reduce it.

The following case presents a problem in diagnosis and treatment not infrequently seen in any hospital. A 47 year old man was brought into the emergency room with the history of having a severe, almost exsanguinating hemorrhage one hour previously, vomiting large amounts of blood and passing blood by rectum. On his admission to the hospital he reacted well to blood replacement, but in several

hours his blood pressure began to drop again and later he vomited blood in large amounts. Improvement again occurred on the administration of transfusions.

It was decided to explore the abdomen, although medical consultants did not look favorably on this decision. On exploration a tumor was found on the posterior upper aspect of the stomach projecting from the serosa, much like a door knob from a door. This slide shows the tumor, which was a leiomyoma. Microscopic resection revealed no evidence of malignant neoplastic changes.

As one can see from the second slide, there is an ulcer on the mucosal side of the lesion through the center of the tumor. It is fairly well agreed, I believe, that hemorrhage, once starting from one of these tumors, does not cease, and probably the only chance for the patient is in surgical extirpation of the lesion.

Although it was not known preoperatively that this patient had a bleeding tumor, nevertheless, on the basis of the criteria that had been set up by Dr. Brown, he would have been a candidate for operation because he was in the right age group and also had severe or exsanguinating hemorrhage of classes 3 and 4. Consequently, I think that Dr. Brown has outlined some valuable criteria for us in the surgical exploration of massive hemorrhage.

Dr. Rudolph J. Noer, Detroit: The paper presented by Dr. Brown is of particular interest in that it represents a cooperative study between the departments of medicine and surgery. I am sure we would all agree with the statement that patients with massive hemorrhage, those with recurrent hemorrhage and older patients who are of such an age that they do not stand hemorrhage well should be treated by gastric resection before they reach a stage at which they might be called moribund. Yet all of us have had the experience of being called to see patients long after the optimum time for resection had passed.

For the past three years there has been a combined meeting of representatives of the departments of medicine and surgery in the Detroit Receiving Hospital. This group, with their residents, together see all the problem cases and the difficult diagnostic problems in the gastrointestinal field in both medical and surgical services. The cooperative consideration and discussion have resulted in a much greater understanding between the two groups. The internists have learned what surgery has to offer, and the surgeons better understand the internists' viewpoint.

As a result, we no longer have to wait until the patients are moribund before they are referred for operation. Furthermore, we no longer meet with the same reluctance to adopt the program of massive blood replacement, nor do we find opposition to the use of gastric suction to place the stomach at rest immediately after the patients' admission to the hospital. I am sure such cooperative studies might well be extended to other fields, to the great benefit of our patients.

Dr. J. Dewey Bisgard, Omaha: I have had experience with 26 primary gastric resections for perforated lesions of the stomach and duodenum, with soiling of the peritoneal cavity, and three simple closures combined with vagotomy for the same condition. Most of these procedures fall into a group which we may classify as elective, but I believe that there are two types of lesions with absolute indication for resection. I can best illustrate these types with slides.

(Slide) This first one represents an elective resection in a young man, only 26, with a long life expectancy and with a likelihood of difficulty from recurrent ulcers in the future if only simple closure had been done. Perforation had occurred only two hours previously, with a minimal amount of soiling, probably no more than occurs occasionally while a routine resection is being done.

(Slide) This is the resected specimen and shows a perforated ulcer just beyond the pylorus and a second kissing ulcer on the posterior wall.

(Slide) This is the specimen opened, showing the two ulcers.

(Slide) One of the absolute indications for a primary resection is this case of perforated carcinoma. You cannot expect sutures to hold a perforated carcinomatous ulcer, and of course the underlying disease is not affected unless resection is performed. This Negro waiter, aged 49, was operated on five hours after perforation of the carcinomatous crater.

(Slide) He lived twenty months and worked for one year after operation and died finally of carcinomatosis. Here is the resected specimen, with perforation at this point. Obviously this was not the usual type of ulcer because the wall was extensively indurated about the area of perforation, so a biopsy was taken and on frozen section was found to be carcinoma.

Here are the big ulcerating lesions, two of them with infiltration of the wall with carcinoma.

(Slide) The other cases in which resection is absolutely indicated are those in which hemorrhage takes place simultaneously with perforation. In these cases there is more than one ulcer, and the anterior one perforates but is not the one from which bleeding occurs. Bleeding occurs from a posterior ulcer, as a rule, or one located somewhere else; so simple closure of the perforation does not control the hemorrhage. A review of the literature shows that in most cases in which simple closure has been done exsanguinating hemorrhages have later occurred, so that primary resection is indicated to control the bleeding.

(Slide) Here is the resected specimen showing the perforation on the anterior wall.

(Slide) This shows the ulcer on the posterior wall from which hemorrhage occurred.

Dr. John Reid Brown, Detroit: We have had some less common causes of massive hemorrhage which were not talked about much in this paper because of the lack of time. There were two patients who had perforation and hemorrhage of a massive nature, both of whom were treated by resection and both of whom recovered. We also encountered some benign tumors and some of the less frequent causes of hemorrhage.

The most important thing we have learned, however, is to admit patients with massive hemorrhage directly to the surgical service and then refer them to the medical service if they do not present immediate problems. In this way we can pick out patients who are going to require operation. We feel that the classification of patients into four groups when they are first admitted to the hospital is probably the most important factor in helping us to decide which ones will require operation.

Dr. Lester R. Dragstedt, Chicago: I should like to make one additional comment about the insulin test. As we have had more experience with this method of examination in the clinic and in the laboratory, we have become persuaded that a positive reaction to the insulin test means that the vagus nerves to the stomach have not been completely divided. There is not time to discuss the results of vagotomy in the treatment of ulcer, but I should say that in our experience recurrence or failure to heal has been almost always associated with an incomplete vagotomy, as evidenced by the insulin test.

In the presence of a positive reaction to the insulin test about two thirds of the patients remain well. I think we have now a partial explanation for this phenomenon. The insulin test apparently is a profound stimulus to the vagus secretory nerves. If one makes a Pavlov pouch after the method described by Pavlov, the

insulin reaction is invariably positive. Nevertheless, they have little or no nervous secretion of gastric juice, as is evidenced by the fact that if quantitative studies of their gastric juice output for long periods are made and then the vagus nerves divided the output may not be reduced at all, indicating that the stimulus of the sight and odor and taste of food is not as strong as the stimulus of insulin hypoglycemia.

I have become convinced that a negative insulin reaction immediately after operation, followed by a positive reaction from six weeks to three months subsequently, does not mean that the vagus nerves have regenerated but rather that traumatized vagus nerves that have not been divided have recovered from the trauma and are able to convey secretory nerve impulses.

It is striking how little gastric juice in some instances may provoke a typical peptic ulcer. Perhaps that is best illustrated in the occurrence of a peptic ulcer in Meckel's diverticulum. All of you have doubtless seen instances of this phenomenon.

In these cases an exceedingly small remnant of heterotopic gastric mucosa in the Meckel diverticulum may suffice to produce a large, chronic peptic ulcer in the ileum. We do not know whether this heterotopic mucosa in the ileum has vagus innervation or not. We know that the vagi go down to the ileum. Probably there are secretory fibers to this heterotopic mucosa.

It is not surprising, then, that we occasionally see recurrence of peptic ulcer after almost complete gastric resection, when the small remnant of the fundus of the stomach discharges acid gastric juice into a tissue such as the esophagus or the jejunum, which has less resistance to its corrosive action.

It has seemed to me that the fact that we do find recurrence of stoma or duodenal ulcer in the presence of a small amount of gastric juice in an occasional case does not mean that we should abolish the secretion of gastric juice entirely in all patients with peptic ulcer. Clearly, if that were desired or required, a total gastrectomy would be the logical operation for all ulcers. In the great majority of cases our experience has taught us that it is not necessary to abolish the secretion of gastric juice entirely. It is sufficient to abolish the hypersecretion, which in the presence of duodenal ulcer is exclusively nervous in origin. This is the physiologic basis for vagotomy.

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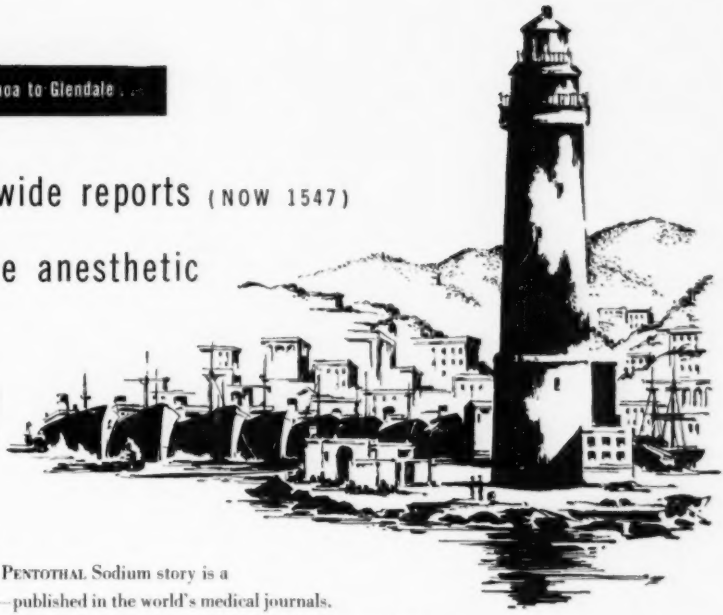

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